American Heart Journal

An international publication for the study of the circulation

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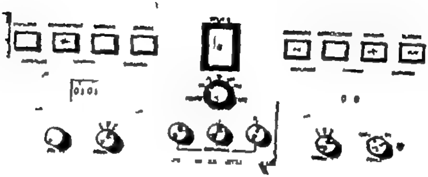

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American Heart Journal

July, 1968 Volume 76 Number 1

Editorial

The relation between metabolic acidosis and cardiac arrhythmias in acute myocardial infarction

R. Anderson, M.B.
London, N.W. 3, England

Until recently, the mortality rate in myocardial infarction had remained virtually unchanged in the past 30 years, varying between 30 and 40 per cent. With the advent of the coronary care unit, it has become possible to increase the patients' chance of survival partly by the more energetic treatment of cardiogenic shock, but largely by the prevention or reversal of death-producing arrhythmias. In one such unit[1] the mortality rate was 12 per cent of 130 consecutive patients and in only two instances of complete heart block was it possible to attribute the cause of death to a disturbance of rhythm. This striking improvement was achieved by the immediate recognition and prompt suppression of the minor arrhythmias which are such a common feature of the early phase of acute myocardial infarctions. Their prevention would therefore be an important factor in improving the prognosis in this disease.

It has been shown in the past that patients with hypotension and pulmonary congestion following a myocardial infarction may have a metabolic acidosis in the first 24 hours following the onset of pain.[2,3] Experimental and clinical experience suggests that metabolic acidosis may be a factor in producing arrhythmias, even where respiratory compensation has resulted in a normal arterial pH.

Ledingham and Norman showed that in experimentally induced cardiac arrest when the accompanying acidosis was not corrected, post-arrest arrhythmias invariably occurred. In those animals in whom the metabolic acidosis was carefully corrected, the incidence of arrhythmias was markedly reduced, even where a respiratory acidosis was superimposed by ventilating the animal with carbon dioxide mixtures. Gerst and associates[4] have shown that metabolic acidosis results in a reduced threshold for ventricular fibrillation while metabolic alkalosis protects the heart from this arrhythmia. Respiratory alkalosis and acidosis did not alter the fibrillation threshold, nor did the superimposition of respiratory alkalosis on metabolic acidosis return the fibrillation threshold to normal.

In experimentally induced extreme acidosis, a characteristic sequence of electrocardiographic changes, sinus tachycardia,

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electrical alternans, 2 to 1 block, complete heart block, and asystole has been described,[3] with reversal of the sequence on correcting the acidosis. A similar sequence was seen in clinical practice. Brooks and Feldman[4] have also described arrhythmias accompanying a postoperative metabolic acidosis, with reversion to sinus rhythm following infusion of alkali. Harden and associates[5] described a case of ventricular fibrillation which failed to respond to repeated countershocks but when the accompanying metabolic acidosis was corrected, spontaneous reversion to sinus rhythm occurred.

These findings suggest that metabolic acidosis which is known to occur in the early stages of an acute myocardial infarction may be a factor in the development of arrhythmias, although the degree of this acidosis is far less than that encountered in the clinical and experimental situations described, unless there is also profound cardiogenic shock.

With this in mind, a group of 21 patients have been studied, all of whom presented with persistent ischemic cardiac pain. Diagnostic serial electrocardiographic changes and raised serum enzymes were present in all cases. The heart rate and rhythm were monitored for at least 72 hours and one-minute electrocardiograph (ECG) recordings were made hourly. Arterial blood samples were obtained by brachial artery puncture on admission and at the onset of any arrhythmia. An ECG recording was made at the same time and the patient's blood pressure was also noted. The arterial blood pH and base deficit were measured by the Astrup microelectrode technique. Since, as a result of compensatory mechanisms, a severe metabolic acidosis may be accompanied by only a minor reduction in blood pH, metabolic acidosis was assessed on the value of the base deficit rather than the actual pH of the blood sample. The patients were graded on the basis of their history and their clinical and ECG findings according to the Peel prognostic index.[6]

Metabolic acidosis was present in nine patients on admission, as shown by a base ore than 2.5 mEq. per liter ted with hypo- mia

nied by a higher prognostic index and a poor early prognosis. Acidosis was not associated with a significantly increased incidence of arrhythmias on admission, but further episodes of arrhythmia in the first three days were much commoner in these patients. Three patients with cardiac arrhythmias had a marked base deficit corrected by intravenous infusion of sodium bicarbonate. The patients' general condition improved, but the arrhythmia continued and had to be corrected by other means. The range of arrhythmias was wide in all the patients studied, with ventricular premature contractions predominating. Ventricular fibrillation and asystole resulting in circulatory arrest were predictably always accompanied by acidosis. The only minor arrhythmia invariably accompanied by metabolic acidosis was sinus bradycardia, present in three cases. This arrhythmia frequently accompanies experimental acidosis and clinical shock, and Peretz and associates[7] have suggested that this may be due to an accumulation of acetylcholine, since cholinesterase functions best at a pH of 7.5 to 8.5 and is inhibited at a lower pH. A total of 21 samples were obtained from 12 patients who developed episodes of arrhythmia after admission. There appeared to be no close correlation between the onset of an arrhythmia and the patient's acid-base state at the time. The relation between the presence of metabolic acidosis and the patient's blood pressure at the time is of interest. Of the eight with metabolic acidosis, seven were hypotensive at the time, while of the 13 remaining, two patients were hypotensive at the time. This suggests that where metabolic acidosis occurs at the time of an arrhythmia it is probably as a result of circulatory insufficiency rather than the cause of the arrhythmia itself.

The close association of metabolic acidosis with hypotension is the outstanding feature of these results. Metabolic acidosis is also associated with a poor early prognosis and its incidence rises with a rising prognostic index. The presence of metabolic acidosis is thus a reflection of the severity of the infarct. The apparent predisposition of patients with metabolic acidosis to develop arrhythmias is probably

related to the greater severity of their illness rather than a direct result of the acidosis, particularly since correction of the acidosis although improving the patient's general condition does not correct the arrhythmia

REFERENCES

1 Anderson, R., Gardner F V Honey H Noble, I and Woodgate, D W Proceedings of the British Cardiac Society Brit Heart J 29:937 1967
2 Astrup, P Jorgensen K, Andersen, O. S., and Engel, K. The acid-base metabolism, Lancet 1 1035 1960.
3 Brooks, D K., and Feldman, S. A. Metabolic acidosis. A new approach to neostigmine resistant curarisation, Anaesthesia 17:161 1962
4 Gerst P H Fleming, W H and Malm, J R. A quantitative evaluation of the effects of acidosis and alkalosis upon ventricular fibrillation threshold, Surgery 59 1050, 1966.
5. Harden, K Mackenzie, I L., and Ledingham I McA. Spontaneous reversion of ventricular fibrillation, Lancet 2:1140, 1963.
6 Kirby B. J and McNichol M W Acid-base status in myocardial infarction, Lancet 2 1054 1966.
7 Ledingham, I McA and Norman J N Acid base studies in experimental cardiac arrest, Lancet 2:967 1962.
8. Low B., Fakhro, A. M Hood, W B and Thorn, G W The coronary care unit, J.A M.A. 199 188, 1967
9 Mackenzie G. J Taylor S H Flenley D C Macdonald, A. H Staunton, H P and Donald K. W Circulatory and respiratory studies in myocardial infarction, Lancet 2:825 1964
10. Neaverson, M A. Metabolic acidosis in acute myocardial infarction, Brit. M J 2:383 1966.
11 Peel A. A. F Semple, T Wang, I Lancaster W M., and Dall, J L. G A coronary prognostic index for grading the severity of infarction, Brit. Heart J 24 745 1962
12 Peretz, D I Scott, H. M Duff J Dossetor J B and MacLean L. D The significance of lactacidaemia in the shock syndrome, Ann. New York Acad Sc. 119 1133 1965.
13. Stewart, J S. S Stewart, W K., Morgan H G and McGovern S. W A clinical and experimental study of the electrocardiograph changes in extreme acidosis and cardiac arrest, Brit. Heart J 27:190, 1965

Clinical communications

Unusual diastolic murmurs in constrictive pericarditis and constrictive endocarditis

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Diastolic murmurs occur rarely in cardiac constriction When present they usually indicate co-existent but unassociated conditions. We wish to present three unusual patients, two with constrictive pericarditis and one with constrictive endocarditis in whom diastolic murmurs were a *prominent* feature of the examination

Case reports

Case 1 W O a Negro man 32 years of age had an acute illness of three days duration, pyrexia, left-sided pleuritic pain dyspnea, cough and sputum. For 14 years, he had suffered from cough and sputum particularly in the winter On two occasions, six and four years previously he had been treated in hospitals for pneumonia. On the initial examination elsewhere, he was ill with a temperature of 103° F and signs of a left-sided pneumonia, with a polymorphonuclear leukocytosis. Jugular venous distention, *hepatomegaly pericardial friction* rub, and a *triple rhythm* were noted Jaundice was present and the blood culture was positive for pneumococci. The x-ray showed bilateral pleural effusions and a calcified pericardium.

After a course of penicillin, the lung condition cleared but signs of cardiac constriction persisted. Antituberculous therapy was given and after two months he was transferred to the *Cardiac Clinic* for further study

On examination, marked jugular venous distension with brisk X and Y descents and hepatomegaly were noted. The blood pressure was 100/60 mm *Hg* and a *pulsus paradoxus* was *present Marked* diastolic pulsation characteristic of cardiac constriction could be seen and felt. There was an early third heart sound and sudden inspiratory splitting of the second heart sound There were two unusual findings, however (1) a dominant A wave was present in the neck, and (2) a diastolic murmur in the fourth left parasternal space accentuated on inspiration was clearly audible (Fig 1).

The electrocardiogram (ECG) (Fig 2 *A*) showed right axis deviation (+110°) a bifid wide P wave and ST T wave abnormalities. On x-ray calcification of the pericardium most marked in the A-V groove (Fig 3 *A*) was present. A diagnosis of calcific constrictive pericarditis with acquired tricuspid stenosis was made.

The findings at cardiac catheterization are shown in Table I A small diastolic gradient was noted across the tricuspid valve (Fig 4 *A*) but there was no mitral valve gradient. The catheter findings confirmed the clinical diagnosis.

After several weeks treatment with antituberculous drugs, digitalis, and diuretics without any alteration in the physical signs the patient was submitted to surgery (Dr T O Donovan). Pressures could not be recorded The pericardium was found to be adherent and densely calcified on the diaphragmatic *surface and around the left pulmonary veins. There* was no obvious constriction in the atrioventricular groove where the pericardium stripped easily ventricular action improved. The postoperative course was smooth The *immediate postoperative* clinical findings were little altered as is usually the case venous hypertension decreased only slightly while the auscultatory findings persisted

From the Cardiac Clinic, Department of Medicine Groote Schuur Hospital, the University of Cape Town and the Cardiovascular Pulmonary Research Group.
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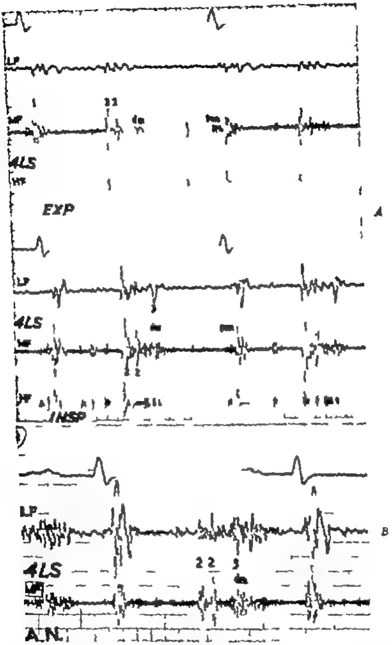

Fig. 1. Phonocardiograms taken at the fourth left intercostal space on expiration and inspiration (A) and after amyl nitrite inhalation (B). The presystolic and mid-diastolic murmurs and the third heart sound promptly intensify on inspiration and after amyl nitrite inhalation. Note the wide splitting of the second heart sound and the abnormal bifid P wave (paper speed 100 mm. per second). *LF*, *MF* and *HF* refer to low frequency, medium frequency, and high frequency, respectively.

Case 2. E. L., Negro man [illegible] years of age, first presented in September, 1966. He had been in ill health for seven months, starting with productive cough and followed by dyspnea on effort, fatigue, and orthopnea. He had also noticed burning pain in both thighs which came on with effort and was relieved by rest. On examination, the signs of cardiac constriction were present. The jugular venous pressure was moderately elevated with brisk X and Y descents, and the liver was enlarged. The blood pressure was 130/80 with marked pulsus paradoxus (at least 15 mm. Hg). The apex was impalpable. A third heart sound and sudden inspiratory splitting of the second sound could be heard. The same two unusual findings reported in Case 1 were present, namely, dominant A waves in the jugular

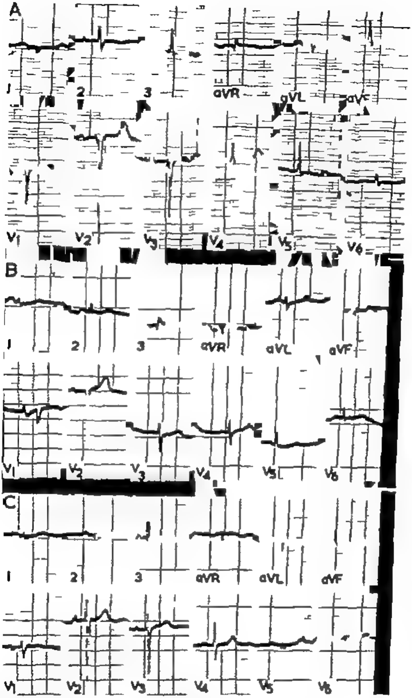

Fig. 2. *A* and *B*, ECGs from Patients 1 and 2, respectively, with constrictive pericarditis. *C*, ECG from Patient 3 (See text). Digitalis has been administered in all three patients.

a diastolic murmur with presystolic accentuation increasing with inspiration and after amyl nitrite inhalation (Fig. 5) both at the mitral and tricuspid areas but maximal at the latter. The ECG (Fig. 2, *B*) showed low voltage in the limb leads and right axis deviation (+110°), abnormal P waves, but no abnormal T wave inversion. The x-ray showed calcification of the pericardium (Fig. 3, *B*) with hilar congestion. A diagnosis of constrictive pericarditis with acquired tricuspid stenosis was made.

The findings at cardiac catheterization are shown in Table I. Simultaneous left ventricular and wedge pressures showed no gradient across the mitral valve, whereas simultaneous right ventricular and

Fig. 3. *A*, A-P and lateral x-rays of Patient 1 showing the dense calcific pericarditis. The annular appearance is better seen in the lateral view. *B*, X-rays of Patient 2. The calcification is similar but less dense. The heart is also larger.

Fig. 3C. X-ray of Patient 3. Note the normal-sized heart with bilateral pleural effusions and marked hilar congestion.

right atrial pressures showed a constant but slight gradient across the tricuspid valve (Fig. 4, *B*) supporting the clinical diagnosis.

Case 3. E. M., a Bantu woman 28 years of age, was admitted complaining that for 3 years she had had swelling of the legs and dyspnea on effort which lately progressed to orthopnea with occasional attacks of paroxysmal nocturnal dyspnea. At the onset of the illness she complained of vague pain in the right side of the chest that occurred on walking.

On examination, marked jugular venous distension (+20 cm.) with poor X and Y descents and a hepatomegaly was found. The blood pressure was 105/70 with only slight pulsus paradoxus. Palpation showed very little pulsation at the apex and no cardiomegaly. Several murmurs were present, the most striking being a middiastolic (Fig. 6) at the fourth left space, increasing on inspiration, highly suggestive of tricuspid stenosis. A soft early diastolic murmur of aortic incompetence was present

Table 1

	H O		R. L.		K. M	
	Mean (*mm Hg*)	*Pressures* (*mm Hg*)	*Mean* (*mm. Hg*)	*Pressures* (*mm Hg*)	*Mean* (*mm. Hg*)	*Pressures* (*mm Hg*)
R.A.	16	18 18 x15 y10	9	11.5 9 x3 y6	18	a21 v20 17 y17
R.V		37/6–22		21/7 14		32/14 16
M P A	25	36/19	13	21 11		47/25
R P C W	18 5	a22 22 16 y16	11 5	12.5 13.5 7 5 y7	30	a32, v39 x24 y22
P P		7 5		15		5
C I		2 1		1 6		1
P V R.		2		<1		7 4
S V R.		17 5		23		40
L V synchronous wedge and LV pressures		112/10–22 diastolic no gradient		98/5–15 diastolic no gradient		112/12 15 diastolic mean gradient 11 5 mm

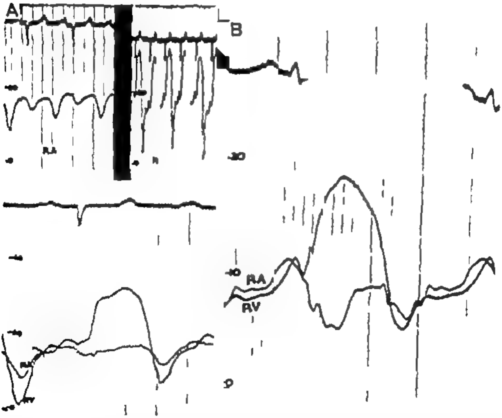

Fig 4 Pressure tracings in the right atrium and right ventricle taken during cardiac catheterization A Patient 1 Note the brisk X and Y descents in the right atrial tracing and the constant but small gradient between right atrial and right ventricle through most of diastole The right ventricular tracing shows the typical marked diastolic dip and *rapid filling characteristic of constrictive* pericarditis. *B* A constant gradient between the right atrium and right ventricle throughout diastole suggesting tricuspid stenosis, is shown in Patient 2

Fig. 5. Phonocardiogram from P tient 2, showing the increase i intensity in diastolic and presystolic murmurs at the fourth left space after the inspiration and amyl nitrite inhalation (A.N.). The sudden wide splitting of the second sound on inspiration can also be seen with the early third heart sound.

t the base. Soft pansystolic, middiastolic, and pre systolic murmurs were heard at the apex and tricuspid opening snap was recorded. The ECG showed right axis deviation (+100°), bifid P waves, and no abnormal T wave inversion (Fig. 2 C). The -ray showed normal-sized heart (Fig. 3 C) which moved poorly on roentgenoscopy with hilar congestion

The findings at cardiac catheterization are shown in Table I. The wedge pressure was far higher than the right trial with mean diastolic gradient of 11.5 mm. across the mitral valve (calculated mitral valve area of 0.6 sq. cm.) and mean diastolic gradient of 4.5 mm. across the tricuspid valve (a calculated tricuspid alve orifice of 1.3 sq. cm.) (Fig. 7). A small aortic valve gradient of 8 mm. was also found. A small gradient of 5 mm. across the pulmonary valve was also encountered. Left ven triculography showed mild mitral incompetence with poor contraction of the left ventricle; aortography revealed mild aortic incompetence. A diagnosis of constrictive endocarditis with multivalvar involvement was made associated constrictive pericarditis was thought to be less likely

A thoracotomy was advised and at operation (Dr. R. Hewitson) the lungs felt stiff. The heart appeared to be restricted by the parietal pericar dium, which was 2 to 3 mm. thick, but there were no intrapericardial adhesions or excessive pericardial fluid. The isceral pericardium appeared normal. A diastolic thrill was present over the right ventricle but not the left. The mitral valve easily admitted one finger (about 3 sq. cm.) Both cusps were thickened, especially the posterior with poor mobility of the anterior cusp. Inadequate apposition of the cusps produced mild regurgitation. The chordae were thickened and fused; the atrial wall appeared hard and thickened. The tricuspid valve was slightly stenosed (admitting 2 fingers), all the cusps and chordae were thickened with reduced mobility and the anterior commissure was fused. A mild regurgitant jet was present. N operation was ttempted on either valve.

The macroscopic appearance was not that of rheumatic heart disease but of chronic endocarditis with some pericarditis. The histologic ppearance of the pericardium as that of uniform fibrous thickening with sparsely scattered nonspecific round cells and occasional multinuclear giant cells. Biopsy of both right and left atria showed endocardial thickening which appeared to be on the basis of organization of mural thrombi, some showing myx oid degeneration. The endocardial lining cells themselves were swollen and some were deeply included within the superimposed endocardium. The muscle fibers ere elongated, with occasional nonspecific round cells. There was nothing to support rheumatic etiology. The final diagnosis was constrictive endocarditis (nonrheumatic) with pericarditis.

Discussion

Diastolic murmurs associated with con strictive pericard tis are extremely rare. Paul and associates[3] in a series of 53 pa tients in 1948 found three cases in whom the pericardium was extensively calcified at necropsy with calcium penetrating into the myocardium and impinging on the mitral valve. In one of these this produced slight mitral stenosis. Eliasch and co-workers described a similar case in 1950. McKusick[4] reviewed the experience at The Johns Hopkins Hospital in 1952 and found absence of murmurs the rule. He quotes a personal communication from Carroll of a mitral diastolic murmur heard in one patient. Seven years later Mounsey[6] described four patients with annular constrict ve pericarditis and clearly demon strated how bands of calcium mainly in the atrioventricular grooves could produce localized cardiac constriction. His fifth

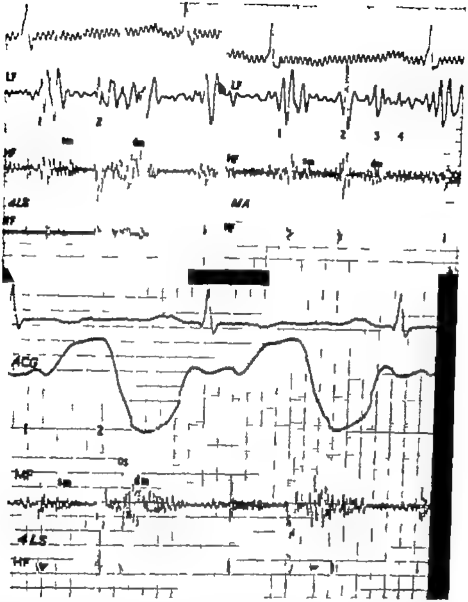

Fig 6 Phonocardiogram from Patient 3 At the fourth left space (*4LS*) the pansystolic murmu and triki g middiastolic murmur of tricuspid alv disease is show At the mitral area, there is pansystolic murmur and a f ll-length diastolic murmur third and fourth heart sounds A synchronou apexcardiogram (*ACG*) and phonocardiogram at the fourth left space show the opening snap of the tricuspid valve preceding the onset of the diastolic murmu t the nadir of the curv t the commencement of left ventricular filling A early systolic ejection sound is also recorded.

patient developed signs of pulmonary mitral and aortic stenosis from external cardiac compression relieved by operation the murmurs lessened but did not completely disappear McGaff and associates[7] described a patient with a middiastolic rumble at the apex a pansystolic murmur at the tricuspid area and a systolic mur mur at the pulmonary area. Cardiac cath eterization demonstrated an acquired in fundibular stenosis with a third chamber but no mitral or tricuspid stenosis. The condition was cured by an operation in which a constricting pericardial band was removed all the signs apart from tricuspid incompetence disappearing Diastolic mur murs can thus be produced either by calcium penetration into the heart producing valve narrowing or by constricting bands particularly *around* the edges of

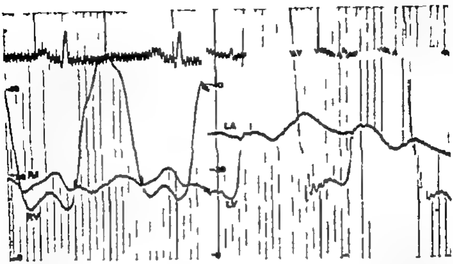

Fig. 7. Right atrial, right ventricular, indirect left atrial, and left ventricular pressure curves taken during catheterization in Patient 3. The left atrial pressure (pulmonary wedge pressure) is far higher than the right atrial. The marked diastolic gradient throughout the whole of diastole is shown across both tricuspid and mitral valves. Note the high enddiastolic pressures in both ventricles; the characteristic diastolic dip, however, is absent.

the ventricular grooves tethering the outflow tracts and interfering with the normal pumping action of the heart.

In either event, these murmurs are extremely rare. Absence of murmurs is the rule and the only patients with murmurs encountered in our first 220 patients with constrictive pericarditis[8] had unrelated valve disease. The first two patients described here, thus present a unique manifestation of the disease. Furthermore, we have not been able to trace a report of another patient in whom the tricuspid valve was affected in this way.

Diastolic murmurs are not as rare in cardiomyopathy. In the presence of left ventricular dilatation and cardiomegaly, the murmur has been described as a low pitched apical "roaring" murmur[6] best heard with the bell of the stethoscope applied lightly to the chest wall. Usually the dominant murmur is that of incompetence, particularly that of the atrioventricular valves. Somers and Williams[11] and Parry and Abrahams[12] stressed the frequency of valve incompetence in endomyocardial fibrosis of Nigeria and this is particularly the case where the right ventricle is affected.[13] In all these conditions, however, the heart is usually significantly enlarged with dilatation of the chambers and heart failure, hence the term "congestive cardiomyopathy."

In constrictive endocarditis, on the other hand, there is marked decrease in cardiac compliance without increase in heart size and valve involvement with subsequent murmurs is rare. Amyloid and hemochromatosis are the best recognized causes. McKusick and Cochran[14] and Goodwin and associates[15] heard no murmurs in their patients. Wasserman and co-workers[3] and Clark, Valentine and Blount[ ] found soft systolic murmurs only. However, Cunnar and associates[16] described a blowing systolic murmur and a late rumbling apical diastolic murmur in their patient. At necropsy, mitral stenosis was present due to amyloid infiltration of the heart.

Our patient represents a unique form of endocarditis with involvement of all four valves, poor sluggish ventricular contraction, chronic congestive failure, and pericardial thickening. A normal heart size with marked reduction in ventricular compliance and valve murmurs due to associated involvement of the valve structures characterized the condition.

Summary

Three patients with unusual diastolic murmurs are described. Two with con-

strictive pericarditis presented with the murmurs and hemodynamic findings of tricuspid stenosis attributed to localized constriction of the valves. The third presented with mitral tricuspid and aortic valve murmurs chronic congestive cardiac failure, and a normal-sized heart. Catheterization study and the findings at operation indicated an atypical form of constrictive endocarditis as the cause

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REFERENCES

1. Schrire, V Clinical cardiology London, 1966, Staples Press, p. 319
2. Beck, W Schrire, V and Vogelpoel, L. Splitting of the second heart sound in constrictive pericarditis with observations on the mechanism of pulsus paradoxus, Am. Heart J 64 765 1962.
3. Paul, O Castleman, B., and White, P D Chronic constrictive pericarditis. A study of 53 cases, Am. J M Sc. 216:361 1948.
4. Eliasch, H., Lagerlof H and Werko, L. Diagnosis of constrictive pericarditis with special reference to heart catheterization, Nord. Med. 44 1128 1950.
5. McKusick, V A. Chronic constrictive pericarditis. Some clinical and laboratory observations, Bull. Johns Hopkins Hosp. 90:3, 1952.
6. Mounsey P Annular constrictive pericarditis with an account of patient with functional pulmonary mitral and aortic stenosis, Brit. Heart J 21:325 1959
7. McGaff C. J Haller J A., Leight, L. and Towery B. T Subvalvar pulmonary stenosis due to constriction of the right ventricular outflow tract by pericardial band, Am. J Med. 34 142 1963
8. Schrire, V Pericarditis with particular reference to tuberculous pericarditis, Australasian Ann. Med. 16:41 1967
9. Burch G. E., and Phillips, J H Methods in the diagnostic differentiation of myocardial dilatation from pericardial effusion Am. Heart J 64:266, 1962.
10. Phillips, J H and Burch G. E. Selected clues in cardiac auscultation, Am. Heart J 63:1 1962.
11. Somers, K. and Williams, A. W The phonocardiogram in endomyocardial fibrosis, Brit. Heart J 22:546, 1960.
12. Parry E. H. and Abrahams, D G The function of the heart in endomyocardial fibrosis of the right ventricle, Brit. Heart J 25:619 1963
13. Abrahams, D G: Endomyocardial fibrosis of the right ventricle, Quart. J Med. 31:1 1962.
14. McKusick, V A., and Cochran, T H: Constrictive endocarditis, Bull. Johns Hopkins Hosp. 90:90, 1952.
15. Goodwin, J F Gordon H., Holman, A., and Bishop, M. B. Clinical aspects of cardiomyopathy Brit. M J 1:69 1961
16. Wasserman, A. J Baird, C. L., Richardson, D W and Wyso, E. M. Cardiac haemochromatosis simulating constrictive pericarditis, Am. J Med. 32:316, 1962.
17. Clark, G. M V lentine, E., and Blount S. G. Endocardial fibrosis simulating constrictive pericarditis, New England J Med. 254:349 1956.
18. Gunnar R. M., Dillon R. F Wallyn, R J., and Eliaberg E. I: The physiologic and clinical similarity between primary amyloid of the heart and constrictive pericarditis, Circulation 12:827 1955

Normal splitting of the second heart sound in significant valvular pulmonic stenosis

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Abnormally wide splitting of the second heart sound during expiration is a characteristic auscultatory and phonocardiographic finding in patients with valvular pulmonic stenosis. Even when the stenosis is mild, the interval between aortic and pulmonic valve closure in expiration is usually greater than the normal range of 0.01 to 0.04 second.[1-3] The degree of abnormal splitting relates significantly to the level of the right ventricular systolic pressure and has been used as an index of the severity of the pulmonic stenosis.[1,4]

Normal splitting of the second heart sound is considered presumptive evidence of the absence of significant pulmonic stenosis. This report presents two patients with moderate and severe valvular pulmonic stenosis, respectively, who had normal splitting of the second sound during expiration and inspiration.

Case reports

Case 1. D. S., a 9-year-old girl, was admitted to Montefiore Hospital on Sept. 6, 1966, for cardiac catheterization. Growth and development had been normal. The patient had no cardiorespiratory symptoms and normal exercise tolerance. A prominent cardiac murmur had been present since birth. On admission, physical examination revealed a well-developed, well-nourished child, with no cyanosis, clubbing, or dyspnea. The blood pressure was 90/60 mm. Hg, the pulse was 80 per minute and regular, the respirations were 16 per minute. There were no signs of congestive heart failure. The lungs were clear. The heart was in regular rhythm with the apical impulse in the fifth intercostal space, midclavicular line. A left parasternal systolic heave and a systolic thrill at the left sternal border in the second and third intercostal spaces were present. The first heart sound was normal. The second sound was physiologically split, with normal respiratory movement. The aortic component of the second sound (A_2) was normal, the pulmonic component (P_2) was reduced in intensity. There was a Grade 4/6 harsh, ejection systolic murmur loudest at the second left intercostal space with good transmission into the neck and over the precordium. The rest of the examination was normal.

An electrocardiogram (ECG) showed a normal sinus rhythm, with an axis of +90 degrees, an R/S ratio of 2.1 in V_{4R} and V_1, prominent 2 mm. P waves in Leads II, III, and V_1, and upright T waves in the right precordial leads. The interpretation was right ventricular hypertrophy.

A phonocardiogram confirmed the auscultatory findings (Fig. 1). A right-sided ejection systolic murmur running through A_2 but stopping before P_2 was recorded most prominently in the second left intercostal space. The configuration of the ejection systolic murmur as determined by the Q-peak of the murmur interval of 0.314 second suggested significant pulmonic stenosis. There was normal splitting of the second heart sound, with the A_2-P_2 interval varying from 0.03 second during expiration to 0.07 second during inspiration.

A cardiac series revealed moderate prominence of the pulmonary artery and was suggestive of right ventricular enlargement.

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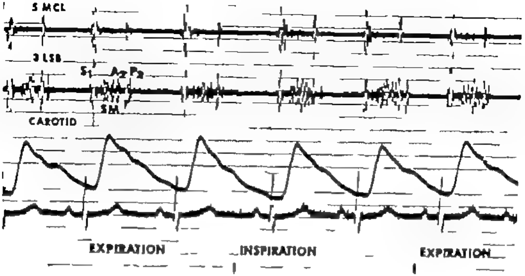

Fig *1* P tient D S. Phonocardiogram recorded t the fifth midcla icular line (*5 MCL*) and the third inter costal space left sternal border (*3 LSB*) during continuous spontaneous respiration with an indirect carotid tracing and Lead 2 ECG There is normal splitting of the second sound, w th the A_2-P interval arying from 0.03 t 0.07 second. The systolic murm is a right-sided jection murmur running through A_2, but topping before P_2. S_1 First heart sound *S31* systolic murmur A aortic alv losure P pulmonic valve closure. Paper speed is 50 mm per second T me lines are 0 01 second.

The clinical impression was significant valv lar pulmonic tenosis, in spite of the normal splitting of the second sound

On Sept. 9 cardiac catheterization was per formed There was no oxygen step-up on right sided screening The rest ng right ventricular pressure was 92/7 mm. Hg, the resting pulmonary artery pressure was 22/10 The 70 mm Hg systolic gra dient was across the pulmonic al e Cineangiogram revealed alv lar pulmonic stenosis, with questionable nf ndibular narrowing

Comment The presence of physiologic splitting of the second sound was difficult to explain in this patient. All other clinical criteria indicated that there was significant valvular pulmonic stenosis. The right ven tricular systolic pressure of 92 mm. Hg and the systolic pulmonic valve gradient of 70 mm Hg proved that moderate val vular pulmonic stenosis was present

Case 2 A. H 4-y ar-old girl, was dmitted t Montefiore Hospital on April 13 1964 for ardiac catheterization. A murmur had been present since birth. Growth and dev lopment had been normal There were no cardiac symptoms and no limitation of activity On admission examination the child appeared comfortable and normally developed. N cyanosis or clubbing w present. The blood pressure was 100/70 mm. Hg the pulse was 100 per minute and regular There were no signs of congestive heart failure the lungs were cle The heart was in regular mus rhythm with the pical im pulse in the fifth intercostal pace just outside the midcla icular line A left parasternal systolic heav was present There was systolic thrill in the second and th rd left i tercostal spaces t the left sternal border The first heart sound was normal A ejec tion click was present long the left sternal border There was physiologic splitting of the second sound, w th decreased intensity of P A Grade 4/6 harsh, ejection systolic murmur was heard over the precordium, loudest at the second left i tercostal space. Examination was otherwise normal.

An ECG showed normal sinus hythm a right xis deviation of +120 degrees, nd R/S ratio of 8/3 in V1 and positi e T waves i the right precordial leads interpreted as right entricular hyper trophy A ectorcardiogram also showed right en tricular hypertrophy

A phonocardiogram (Fig 2) confirmed the auscultatory findings including physiologic splitting of the second sound, w th the A_2-P interval aryi g from 0.03 to 0 07 second d ring respiration. The Q-ejection lick interval was 0 092 second suggest ing significa t pulmonic stenosis The Q-peak of the m rmur i terval was 0 312 second lso suggesting significant pulmonic stenosis.

A cardiac series revealed moderately prominent pulmonary artery nd probable right entricular enlargement.

Though there was phy iologic splitting of the second sound, all other data indicated that ig nificant alvular pulmonic stenosis w present

On April 15 cardiac catheterization was per formed. Oxygen saturation on the right side were normal The resting right entricular pressure w 120/5 mm Hg the resting pulmonary artery pres ure w 18/10 The 100 mm. Hg systolic gradient was across the pulmonic alv Cine ngiogr m

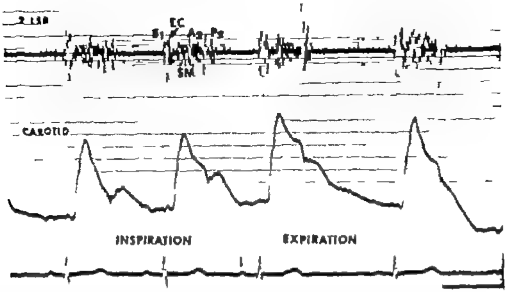

Fig 2 Patient A H. Phonocardiogram recorded at the second intercostal space left sternal border (*2 LSB*) during continuous spontaneous respiration with an indirect carotid tracing and Lead 2 ECG. There is normal splitting of the second sound, with the A_2-P_2 interval varying from 0 03 to 0.07 second. S First heart sound EC ejection click SM systolic murmur A_2 aortic valve closure P_2 pulmonic valve closure. Paper speed = 50 mm. per second Time lines are 0.04 second.

confirmed the presence of valvular pulmonic stenosis

Comment Normal splitting of the second heart sound was present in a patient who otherwise had typical findings of significant valvular pulmonic stenosis. Cardiac catheterization demonstrated severe valvular pulmonic stenosis.

Clinical material and methods of study

The cardiac catheterization data and phonocardiograms of 40 other patients with isolated valvular pulmonic stenosis were reviewed in order to determine the occurrence of normal splitting of the second heart sound with significant stenosis. Cardiac catheterization was performed in standard fashion and the diagnosis was established by accepted clinical hemodynamic, and angiocardiographic criteria. The degree of pulmonic stenosis was related to the resting right ventricular systolic pressure as follows (1) mild pulmonic stenosis, pressure below 60 mm. Hg (2) moderate pulmonic stenosis, pressure between 60 and 110 mm Hg (3) severe pulmonic stenosis, pressure above 110 mm Hg

All phonocardiograms were taken on a four-channel Cambridge photographic recorder at paper speeds of 50 and 100 mm per second utilizing a frequency accentuation filter system with maximum accentuation at 200 c.p.s. The recordings were obtained from the apex, the left sternal border at the third and fourth intercostal spaces and the aortic and pulmonic areas during continuous spontaneous respiration and from the pulmonic area at the beginning of held inspiration and expiration A simultaneous Lead II ECG and indirect carotid pulse pressure tracing were recorded for timing reference. The components of the second sound were identified by their relation to the dicrotic notch of the carotid tracing and their movement during respiration. The aortic component usually preceded the dicrotic notch by 0 02 to 0.03 second.

A total of 30 patients had moderate or severe stenosis. The phonocardiograms of these 30 patients were analyzed.

Results

The phonocardiograms of all 30 patients demonstrated the characteristic features of significant valvular pulmonic stenosis

Table 1 Duration of A_2-P_2 interval during expiration in 30 cases with valvular pulmonic stenosis

Right ventricular pressure (mm Hg)	No. of cases	Range A_2-P_2 interval (sec)
60 to 110	22	0 05 to 0 09
>110	8	0 07 to 0 12

including abnormally wide splitting of the second heart sound during expiration The interval between aortic and pulmonic valve closure during expiration ranged from 0 05 to 0 12 second (Table I) The normal expiratory splitting of the second sound seen in the two patients reported here was not recorded in any of these 30 patients

Discussion

The definite value of the phonocardiogram in the evaluation of the severity of valvular pulmonic stenosis has been well established It has been shown conclusively that the configuration of the ejection systolic murmur the degree of splitting of the second sound and the Q-ejection click interval relate significantly to the severity of the right ventricular hypertension [2] When these three phonocardiographic features are used in combination a reasonably accurate prediction of the right ventricular systolic pressure and the pulmonic valve area may be made [4]

Numerous studies have demonstrated the usefulness of the degree of splitting of the second heart sound in estimating the severity of pulmonic stenosis. Leatham and Weitzman[1] recorded an expiratory split of the second sound of 0 05 to 0 14 second in 33 patients with valvular pulmonic stenosis and right ventricular systolic pressure above 50 mm. Hg Vogelpoel and Schrire[3] obtained second sound splitting during expiration of 0 05 to 0 10 second in 29 patients with a right ventricular pressure greater than 60 mm. Hg Dimond and Benchimol recorded expiratory splitting of the second sound of 0 04 second in one patient with a systolic gradient across the pulmonic valve of 60 mm. Hg In 16 other patients with a systolic gradient greater than 50 mm. Hg the width of splitting during expiration varied from 0 05 to 0 12 second Gamboa and associates[4] reported an expiratory duration of the A_2-P_2 interval corrected for heart rate of 0 054 to 0 177 second in 36 patients with a right ventricular pressure above 80 mm Hg These observations suggest that normal splitting of the second heart sound is a reliable indicator of the absence of significant pulmonic stenosis.

However the present report demonstrates that normal splitting of the second sound may occur in the presence of moderate to severe valvular pulmonic stenosis. The wide splitting of the second sound in valvular pulmonic stenosis has been attributed to delayed pulmonic valve closure secondary to prolongation of right ventricular systole and to lengthening of the protodiastolic phase due to the low pressure above the pulmonic valve. [3,4,7] Significant dilatation of the pulmonary artery even in the absence of pulmonic stenosis, may also delay closure of the pulmonic valve.[8] The two patients reported here had relatively high pulmonary artery pressures for their degree of stenosis. This may have shortened the protodiastolic phase and resulted in earlier pulmonic valve closure These two patients also had only moderately dilated pulmonary arteries. The degree of dilatation and elasticity of the pulmonary arteries may also have played a role in earlier valve closure

These observations do not detract from the usefulness of the phonocardiogram in general and the splitting of the second heart sound in particular in the evaluation of the degree of valvular pulmonic stenosis. However they emphasize that the possibility of exceptional cases must always be considered

Summary

Normal splitting of the second heart sound in two patients with significant valvular pulmonic stenosis is described In 30 other patients with moderate to severe valvular pulmonic stenosis, second sound splitting was abnormally wide A normal expiratory duration of the A_2-P_2 interval has been considered a reliable

indicator of the absence of significant pulmonic stenosis. This report demonstrates that exceptions to this rule may occur. The possible causes of normal splitting of the second sound with significant valvular pulmonic stenosis are discussed.

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REFERENCES

1. Leatham, A., and Weitzman, D.: Auscultatory and phonocardiographic signs of pulmonary stenosis, Brit. Heart J. 19:303, 1957.
2. Aygen, M., and Braunwald, E.: The splitting of the second heart sound in normal subjects and in patients with congenital heart disease, Circulation 25:328, 1962.
3. Vogelpoel, L., and Schrire, V.: Auscultatory and phonocardiographic assessment of pulmonary stenosis with intact ventricular septum, Circulation 22:55, 1960.
4. Gamboa, R., Hugenholtz, P. G., and Nadas, A. S.: Accuracy of the phonocardiogram in assessing severity of aortic and pulmonic stenosis, Circulation 30:35, 1964.
5. Dimond, E. G., and Benchimol, A.: Phonocardiography in pulmonic stenosis: special correlation between hemodynamics and phonocardiographic findings, Ann. Int. Med. 52:145, 1960.
6. Hoffman, J., Rudolph, A. M., Nadas, A., and Paul, M. H.: Physiologic differentiation of pulmonic stenosis with and without an intact ventricular septum, Circulation 22:385, 1961.
7. Hauwaert, L. Vander: DeTweede Harttoon, Brussels, 1963, Arsca Uitgaven, N. V.
8. Schrire, V., and Vogelpoel, L.: Role of the dilated pulmonary artery in abnormal splitting of the second sound, Am. Heart J. 63:501, 1962.

Digitalis for congestive heart failure with heart block in acute myocardial infarction

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Digitalis and bed rest have been the primary therapeutics for the treatment of congestive heart failure since 1785.[1] The use of digitalis preparations for heart failure during acute myocardial infarction has often been thought to be contraindicated because of the threat of arrhythmias. Continuous monitoring[2] and the advent of Coronary Care Units[3] for the care of patients with acute myocardial infarction have unequivocally demonstrated the ectopic arrhythmic tendency of the ischemic or infarcted myocardium. The failing myocardium is particularly unstable and prone to the development of ectopic rhythms including unifocal or multifocal ventricular premature beats and ventricular tachycardia.

Furthermore digitalis has been said to be contraindicated in cases of partial or complete heart block because of the action of digitalis in decreasing atrioventricular node conduction.

This study reports the use of digitalis for congestive heart failure in two patients with complete atrioventricular block and one patient with variable second-degree heart block, all of whom manifested congestive heart failure on the first day of an acute myocardial infarction.

Materials and methods

The patients, aged 65 71 and 4 two of whom were men were admitted to the Coronary Care Unit of The Brooklyn Hospital Division of The Brooklyn Cumberland Medical Center on the first day of an acute myocardial infarction and were continuously monitored . Diaphragmatic (inferior) infarction was documented by electrocardiograms. The histories, enzyme changes, and clinical courses were indicative of an acute myocardial infarction in each instance. Two patients evidenced complete atrioventricular heart block and one had variable second-degree heart block. All manifested signs of congestive heart failure including cardiomegaly elevated venous pressure and basal pulmonary râles. The ventricular rates varied from 40 to 50 a minute.

Initially intravenous isoproterenol was administered by continuous drip in doses of 1 to 4 mg in 1 000 ml of 5 per cent glucose in water and was gradually increased until there was evidence of ventricular premature beats, ST segment depression or acute distress noted by the patient.

Subsequently 0.5 mg of atropine was administered as a single direct intravenous bolus and repeated in four hours without benefit. Hydrocortisone was also administered in the same fashion in doses of 100 mg A transvenous catheter was passed into the right ventricle for pacing if necessary Since the heart block persisted in the three patients as well as the signs of con

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gestive heart failure they were given 0.8 mg of Cedilanid D intravenously followed by digoxin in doses of 0.25 to 0.5 mg intramuscularly or orally every four hours until digitalization was accomplished. No other medications were given concomitantly.

Results

Within 24 hours, all three patients manifested a return to normal sinus rhythm rates 60 to 82 and lost signs and symptoms of congestive heart failure partially or completely. Depression of atrioventricular conduction did not occur. The P-R intervals after restoration of sinus rhythm were 0.16 second in two patients and 0.18 second in the third.

Discussion

The primary action of digitalis is inotropic, and it directly improves myocardial contractility. The effect of digitalis is greatest in the treatment of the failing heart muscle and much less on the normal myocardium. The glycosides apparently enter myocardial cells and in some unknown manner affect myocardial contractility. There may be improved utilization of high phosphate energy bonds which produce intracellular energy and enhance the force and efficiency of myocardial contraction. The resulting increase in stroke volume may improve coronary blood flow and thereby relieve ischemia of the conduction system via nodal vessels. The increment of blood flow may improve conduction through the atrioventricular node and alleviate heart block.

Another effect of digitalis is to increase the refractory period of the atrioventricular node increasing the sensitivity of the A-V node to vagal action thus slowing the heart and increasing the P-R interval. This effect would seem to contraindicate digitalis in heart block.

The treatment of heart failure, however has previously been reported to result in the disappearance of heart block as reported by Eggleston. Blumgart and Altschule[5] produced a therapeutic effect in 19 patients with different degrees of heart block without noticing an increase in block and in fact observing a decreased P-R interval in some.

The use of thiazide-type diuretics has been reported[6] to terminate heart block associated with acute myocardial infarction on the basis of edema of the conduction system. The depletion of intracellular myocardial potassium by thiazides may function by the same physiologic mechanism as digitalis.

Friedberg[7] suggests that digitalis is of doubtful merit in the presence of complete heart block, and may cause fatal asystole. There is potential danger in the indiscriminate use of digitalis in complete heart block unless one is prepared to pace the ventricle by a transvenous intracardiac catheter.

It is certainly true that an increase in heart rate may improve heart failure in complete heart block. If the block is not alleviated by atropine, steroids, or isoproterenol then internal cardiac pacing may be helpful in the management of heart failure by increasing the ventricular rate.

The heart block which accompanies acute myocardial infarction is usually transient, but is associated with a significant mortality rate from cardiac arrest.[4] The heart block may last only several hours and terminate spontaneously. If the heart block is not reversed by isoproterenol atropine or steroids, and if congestive heart failure is present, it may be successfully treated by digitalis.

The heart block may produce congestive heart failure due to low cardiac output but conversely heart failure itself can conceivably produce heart block. When digitalis improves the cardiac output, the block may thereby disappear and normal conduction may ensue.

The adage remains. There is no contraindication to digitalis when there is an indication.

Summary

1. Three patients on the first day of an acute myocardial infarction with heart block, two complete and one incomplete, and associated congestive heart failure were successfully treated with digitalis preparations.

2. It is possible to conjecture that the digitalis reversed the heart failure and the heart block within 24 hours.

3 When digitalis is indicated there is no contraindication

REFERENCES

1. Withering, W An account of the foxglove and its medical uses, with practical remarks on dropsy and other diseases, London 1785
2. Julian, D J Valentine P A and Miller J Disturbances of rate, rhythms, and conduction in acute myocardial infarction, Am. J Med. 37:915 1964
3. Day H. W A intensive coronary care area, Dis. Chest 44:423 1963.
4. Eggleston, C Administration of digitalis by Eggleston method, J.A.M A. 74 733 1920.
5. Blumgart H. L., and Altschule M D: Should digitalis be administered to patients with preexisting partial heart block? Am. J M. Sc. 198:455, 1939
6. Tolman, L. Prevention of Stokes-Adams seizures with chlorothiazide, Ann. New York Acad. Sc. 111:855 1964.
7. Friedberg, C. K. Disease of the heart, Philadelphia, 1966, W B. Saunders Company p. 364
8. Jackson, A. E., and Bashour F A. Cardiac arrhythmias in acute myocardial infarction. I Complete heart block and its natural history Dis. Chest 51:31 1967

The effects of alpha methyldopa on renal function in hypertensive patients

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Therapy with antihypertensive drugs has frequently been complicated by their adverse effects on renal function. For example, hexamethonium administered intravenously in a single dose decreases urine volume, glomerular filtration rate (GFR) and renal plasma flow (RPF) in the supine position[1] while the chronic administration of oral hexamethonium decreases renal function in the ambulatory state.[2] Similarly a single intravenous dose or chronic oral treatment with guanethidine decreases renal function in both the supine and tilted positions.[3-4]

In contrast Onesti and associates found that methyldopa given as a single intravenous injection lowered arterial pressure in both the supine and tilted positions without any adverse renal effects. Similarly it has been observed that oral methyldopa given to hypertensive patients with either normal or impaired renal function produced no significant decrease in GFR and RPF in the supine position. [9] However the influence of chronic treatment with oral methyldopa on renal function in the tilted position in patients with diastolic hypertension and renal disease has not been determined Since during treatment with methyldopa the greatest reduction in arterial pressure is in the upright and not the supine position we have compared the effects of oral methyldopa on arterial pressure GFR, RPF and renal vascular resistance in the supine and tilted positions in hospitalized hypertensive patients with impaired renal function.

Materials and methods

These studies were performed on 8 patients with essential hypertension selected from the Hypertension Clinic of the Cincinnati General Hospital The investigational nature of the study was explained to each patient and consent to participate was obtained The patients, 7 women and 1 man ranging in age from 36 to 54 years, had had hypertension over periods of 2 to 31 years. The diagnosis of essential hypertension was based on history physical examination urinalysis, rapid-sequence intravenous pyelography and in some cases renal arteriography and determination of urinary vanilmandelic acid All medica

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tions, except digitalis in 3 patients were discontinued for at least 10 days before admission. The patients remained ambulatory throughout their hospital stay and received a regular hospital diet containing 8 to 10 Gm. of salt per day. Arterial blood pressure was taken by the same nurse twice daily in the supine position after at least 30 minutes of bed rest and after standing for 3 minutes.

Measurements of renal function were performed on two occasions after 4 days of placebo administration and after 7 to 13 days of treatment with methyldopa when a clear reduction in diastolic pressure was present. The dose of methyldopa taken by each patient on the day before the second set of renal function measurements ranged from 1 to 2.75 Gm. per day.

The placebo was identical in appearance to a 250 mg. methyldopa (Aldomet) tablet. The total number of tablets taken daily by each patient was the same throughout the study. Patients were not aware of the study design.

Renal function studies. Inulin and para-aminohippurate clearances were determined in both the supine and tilted positions at about the same time in the morning in each patient. Food and fluids were withheld from the preceding midnight until completion of the study. Urine specimens were collected through an indwelling multiholed soft rubber urethral catheter and were terminated with air washouts. After a venous blood and urine sample had been obtained, an intravenous priming dose of inulin (40 mg. per kilogram) and para-

Table I. Effects of placebo and methyldopa on arterial pressure (mm. Hg) measured on the ward*

Patient	Placebo		Methyldopa	
	Supine	Erect	Supine	Erect
R. B.	229/150	198/143	169/114	157/107
R. E.	180/92	154/100	143/79	146/83
I. F.	258/129	225/127	206/120	145/109
H. G.	173/129	162/126	155/100	130/95
M. H.	183/120	156/114	198/118	137/89
F. J.	224/140	230/160	140/86	142/104
H. K.	190/120	190/130	140/100	145/110
L. W.	175/110	170/113	135/89	143/103
Mean ± S.E.	202 ± 11 / 113 ± 6	186 ± 11† / 127 ± 7	161 ± 10‡ / 101 ± 5‡	143 ± 3§ / 100 ± 4§

*Each value represents the average of two measurements taken about 6 hours apart during treatment with either placebo or methyldopa on the day preceding renal function studies.

†p < 0.05 compared with the supine value during placebo.

‡p < 0.01 compared with the supine value during placebo.

§p < 0.01 compared with the erect value during placebo.

aminohippurate (8 mg per kilogram) was administered These substances were then infused into a femoral vein at rates estimated to equal their excretion. A period of 45 minutes was allowed for equilibration during which time the patient sat on a tilt table. In 6 patients, GFR and RPF were measured first in the 40 degree tilt position and then in the supine position. In 2 patients, GFR and RPF were studied first in the supine position and then in the tilted position. Three or four urine collections, each 20 to 30 minutes long with appropriate blood samples were collected in each position and used for measurement of GFR and RPF Arterial cuff pressures were measured every 3 to 5 minutes throughout the entire study

The results presented are based upon the measurements of renal function and arterial pressure made during the last period of urine collection in both the supine and tilted positions at which time urine flow had stabilized Renal vascular resistance (mm Hg per milliliter per minute) was calculated by dividing the mean blood pressure with renal blood flow Mean blood pressure was obtained by adding 1/3 of the pulse pressure to diastolic pressure. Renal blood flow was derived by dividing 100 × RPF with 100–hematocrit. GFR and RPF were corrected to 1 73 square

Table II. Effects of placebo and methyldopa on arterial pressure (mm Hg) measured during renal function studies

Patient	Placebo		Methyldopa	
	Supine	Tilt	Supine	Tilt
R B	233/161	227/175	207/136	176/132
R E.	158/92	134/88	172/112	130/90
I F	239/135	232/136	176/116	152/104
B G	200/140	160/128	176/130	144/107
M H	201/131	186/131	222/119	147/100
F J	219/139	130/90	170/110	159/111
H K.	186/117	182/134	170/129	115/92
L. W	159/110	152/115	131/101	127/97
Mean ± S.E.	199 ± 11 / 128 ± 8	175 ± 14† / 125 ± 10	178 ± 10 / 119 ± 4	144 ± 7‡,‖ / 104 ± 5§‖

Each value represents the average of [illegible] to [illegible] measurements taken at 3 to 5 minute intervals during the final 20 or 30 minute urine collection periods in each position.
†p = 0.05 compared with the supine value during placebo.
‡p < 0.01 compared with the supine value during methyldopa.
§p [illegible] 0.05 compared with the supine value during methyldopa.
‖p < 0.05 compared with the tilt value during placebo.

meters of body surface area. Inulin was determined by the modification by Rolf and co-workers of the method of Alving and associates[11] and para aminohippurate by that of Smith and co-workers.[12]

The paired student t test was used for all the statistical analyses, and p values equal to or under 0.05 were considered significant. Observations in the supine or tilted position during placebo administration were compared with those obtained in the same position during treatment with methyldopa. Also results in the tilted position were compared with those obtained in the supine position during the same treatment periods.

Results

Arterial pressure. Treatment with methyldopa significantly reduced systolic and diastolic pressures measured in both the supine (−41/−23) and standing (−43/−27) positions on the ward the day preceding renal function studies (Table I). Arterial pressure measured in the supine (−21/−9) and tilted (−31/−21) positions during the actual renal function studies were also lower during treatment with methyldopa than during treatment with placebo (Table II). In addition tilting lowered diastolic pressure significantly during treatment with methyldopa whereas, during treatment with placebo tilting did not reduce diastolic pressure (Table II).

Urine volume. The administration of methyldopa was associated with a significant increase in urine volume in both the supine (42 per cent) and tilted (80 per cent) positions compared to that during placebo administration (Table III). However urine volume was decreased by tilting during treatment with either placebo (61 per cent) or methyldopa (50 per cent).

Glomerular filtration rate. GFR was 71 ml. per minute in the supine position and 58 ml. per minute in the tilted position during placebo administration. During treatment with methyldopa, these values were 76 and 66 ml. per minute respectively (Table IV). Treatment with methyldopa was not associated with a reduction in GFR even in those patients who had the lowest filtration rates, i.e. R. B. and M. H. and who showed a reduction in arterial pressure.

Renal plasma flow. Treatment with methyldopa increased RPF from 302 and 233 ml. per minute in the supine and tilted positions to 350 ml. per minute ($p < 0.2$) and 306 ml. per minute ($p < 0.05$) respectively (Table V). Even those patients (I. F. and R. B.) with the lowest RPF appeared to show an increase in RPF. It is of interest that tilting decreased RPF

Table III *Effects of placebo and methyldopa on urine volume (milliliter per minute)*

Patient	Placebo		Methyldopa	
	Supine	Tilt	Supine	Tilt
R. B.	0.63	0.25	1.52	0.27
R. E.	0.41	0.33	0.83	0.43
I. F.	0.65	0.43	0.55	0.4
B. G.	0.8	0.3	1.78	0.85
M. H.	0.57	0.12	0.6	0.3
F. J.	1.68	0.27	1.7	1.1
H. K.	0.85	0.3	0.95	0.28
L. W.	1.05	0.6	1.48	1.05
Mean ± S.E.	0.83 ± 0.14	0.33 ± 0.05	1.18 ± 0.18†	0.59 ± 0.13‡, §

*p < 0.01 compared with the supine value during placebo.
†p < 0.05 compared with the supine value during placebo.
‡p < 0.01 compared with the supine value during methyldopa.
§p = 0.05 compared with the tilt value during placebo.

?3 per cent (p = 0.05) during placebo administration but only 13 per cent (p < 0.3) during treatment with methyldopa.

Renal vascular resistance. Renal vascular resistance was significantly reduced in both the supine and tilted positions, 17 per cent and 42 per cent respectively during treatment with methyldopa (Table VI). During placebo administration, tilting produced a 40 per cent increase (p < 0.1) in renal vascular resistance. In contrast tilting during treatment with methyldopa decreased renal vascular resistance 4 per cent.

Discussion

This study demonstrates that the antihypertensive effect of oral methyldopa in the upright position is associated with an increase in urine volume and RPF in hypertensive patients with renal damage. These effects develop without a concomitant decrease in GFR. Similar results were observed in the supine position con

Table IV. Effects of placebo and methyldopa on glomerular filtration rate (milliliter per minute)

Patient	Placebo		Methyldopa	
	Supine	Tilt	Supine	Tilt
R. B.	57	46	65	44
R. E.	91	93	124	89
I. F.	55	58	48	52
B. G.	72	78	78	74
M. H.	56	25	55	45
F. J.	80	31	59	76
H. K.	63	41	85	51
L. W.	95	93	94	97
Mean ± S.E.	71 ± 6	58 ± 10	76 ± 9	66 ± 7

*GFR was corrected to 1.73 square meters of body surface area.

Table V. Effects of placebo and methyldopa on renal plasma flow (milliliter per minute)

Patient	Placebo		Methyldopa	
	Supine	Tilt	Supine	Tilt
R. B.	212	164	[illegible]38	182
R. E.	420	372	676	425
L. F.	180	172	190	196
B. G.	307	347	331	335
M. H.	248	109	235	191
F. J.	363	150	316	381
H. K.	298	164	330	249
L. W.	390	384	443	491
Mean ± S.E.	302 ± 30	233 ± 40†	330 ± 51	306 ± 42‡

*RPF was corrected to 1.73 square meters of body surface area.
†p = [illegible] compared with the supine value during placebo.
‡p < 0.05 compared with the [illegible] value during placebo.

Table VI. Effects of placebo and methyldopa on renal vascular resistance (mm. Hg per milliliter per minute)

Patient	Placebo		Methyldopa	
	Sup	Tilt	Supine	Tilt
R. B.	0.526	0.703	0.373	0.485
R. E.	0.129	0.132	0.093	0.115
I. F.	0.576	0.596	0.435	0.374
B. G.	0.334	0.265	0.289	0.235
M. H.	0.456	1.007	0.478	0.444
F. J.	0.236	0.354	0.212	0.172
H. K.	0.297	0.377	0.258	0.253
L. W.	0.172	0.177	0.134	0.116
Mean ± S.E.	0.341 ± 0.058	0.476 ± 0.106	0.284 ± 0.049†	0.274 ± 0.051‡

Renal vascular resistance was calculated from measured renal blood flow uncorrected for standard body surface area.
†p < 0.05 compared with the supine value during placebo.
‡ < 0.05 compared with the tilt value during placebo.

firming the findings of previous studies[7, 8] in that position. The increase in RBF in both the supine and tilted positions was associated with a decrease in renal vascular resistance. It may be that the diminished renal vascular resistance and the attendant increase in RPF were large enough to maintain GFR despite a reduction in perfusion pressure. The combination of decreased arterial pressure and renal vascular resistance and increased RPF in association with the previous report that methyldopa does not affect cardiac output[7] suggests that methyldopa may decrease the vascular resistance of the kidney to a greater degree than that of other vascular beds.

The observation that methyldopa abolished the reflex augmentation in renal vascular resistance associated with tilting suggests that at least partial adrenergic nerve blockade was present. This is consonant with the observations of Mason and Braunwald[13] who have reported that oral methyldopa in doses of 2 to 5 Gm. per day either reduced or abolished arterial and venous reflex *vasoconstriction in man*. The finding that methyldopa also decreased renal vascular resistance significantly in the supine position, a position which is thought to be associated with minimal sympathetic reflex activity, suggests that methyldopa may also reduce renal vascular resistance through a mechanism other than sympathetic nerve blockade. This possibility was also suggested by previous studies of Mohammed and Gaffney, in which the chronic administration of methyldopa decreased the vascular resistance of the perfused hindleg of the dog more than did acute surgical denervation or pretreatment with reserpine or guanethidine.

In contrast to the results in the present investigation, Onesti and associates[4] reported that acute intravenous methyldopa significantly decreased GFR in the supine position without an increase in RBF in either the supine or tilted position. The discrepancies between the two studies may be accounted for by the differences in the route of drug administration and duration of treatment and the greater reduction in arterial pressure observed with intravenous methyldopa.

The effects of oral methyldopa on renal function and arterial pressure observed in the tilted position in the present study provide a rational basis for the use of this *drug in the treatment of ambulatory* hypertensive patients with impaired renal function.

Summary

The effects of oral treatment with methyldopa 1 to 2.75 Gm. per day for 7 to 13

days on arterial pressure urine volume glomerular filtration rate renal plasma flow and renal vascular resistance were studied in both the supine and tilted positions in 8 hospitalized patients with sustained essential hypertension and impaired renal function Despite a decrease in arterial pressure during treatment with methyldopa, GFR did not decrease while renal plasma flow increased in the supine and tilted positions from 302 to 350 ml per minute and from 233 to 306 ml per minute respectively A significant increase in urine volume was also observed in both positions. These effects of drug administration were accompanied by a decrease in renal vascular resistance

The results of this study provide a rational basis for the use of methyldopa in the treatment of ambulatory hypertensive patients with impaired renal function.

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REFERENCES

1 Mills, I C., and Moyer J H. The acute effects of hexamethonium on renal hemodynamics in normotensive and hypertensive human subjects, Am J M Sc 226 1 1953.
2. Ford R. V Moyer J H and Spurr C. L. Hexamethonium in the chronic treatment of hypertension—its effects on renal hemodynamics and on the excretion of water and electrolytes, J Clin. Invest. 32 1133 1953
3. Novack, P The effect of guanethidine on renal, cerebral, and cardiac hemodynamics, Hypertension recent advances, The second Hahnemann symposium on hypertensive disease, Philadelphia, 1962, Lea & Febiger p. 444
4 Villarreal, H Exaire J E., Rubio, V and D vila, H. Effect of guanethidine and bretylium tosylate on systemic and renal hemodynamics in essential hypertension Am. J Cardiol. 14:633 1964
5 Richardson, D W Wyso, E. M., Magee J H and Covell G. C. Circulatory effects of guanethidine. Clinical, renal, and cardiac responses t treatment with novel antihypertensive drug. Circulation 22 184 1960
6. Onesti, G Brest, A N Novack, P Kasparian, H and Moyer J H Pharmacodynamic effects of alpha-methyldopa in hypertensiv subjects, Am Heart J 67:32, 1964
7 Sannerstedt, R Rojo, G Varnauskas, E., and Werko, L Alpha-methyldopa i arterial hypertension. Cli ical, renal, and hemodynamic studies, Acta med scandinav 1 4:53 1963
8. Cannon, P J Whitlock, R. T Morris R. C., Angers, M and Laragh, J H. Effect of alpha-methyldopa in severe and malignant hypertension, J.A.M A 179:673, 1962.
9 Weil, M H. Barbour B, H and Chesne, R. B Alpha-methyldopa for treatment of hypertension—clinical and pharmacodynamic studies, Circulation 28 165 1963
10 Roif D Surtabin, A and White, H. L A modified diphenylamine procedure for fructose or in lin determination, Proc. Soc. Exper Biol & Med. 72:351 1949
11 Alving, A S Rubin, J and Miller B. F A direct colorimetric method for the determination of inulin in blood and urine J Biol. Chem. 127:609 1939
12 Smith, H W Finkelstein, N Aliminosa, L Crawford, B., and Graber M The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man, J Clin. Invest. 24:388, 1945
13. Mason, D T and Braunwald, E Effects of guanethidine, reserpine, and methyldopa on reflex venous and arterial constriction in man, J Clin. Invest. 43 1449 1964
14. Mohammed, S and Gaffney T Effect of acute and chronic administration of alpha-methyldopa on flow-pressure curves (Abstract) Cl n. Res. 15:216, 1967

The treatment of myocardial infarction with low molecular weight dextran

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In January, 1962, a study was begun using low molecular weight dextran (LMDx) with an average molecular weight of 41,000* in the treatment of acute myocardial infarction. Its use was based on the presumption that the intravascular sludging consistently observed in the conjunctival capillary bed in acute infarct and first reported by Bloch,[1] which phenomenon is reportedly reversible or preventable by LMDx infusion,[2] might be of some pathologic significance as suggested by the experimental work of Long and associates. Initially, 65 consecutive cases of acute infarction received LMDx by continuous intravenous infusion for the first 76 hours of their treatment program on the same schedule as that listed in the following report. Changes in several laboratory measurements of undetermined significance were noted. Appreciation of the importance of adequate renal function and perfusion for the excretion of LMDx and, therefore, its safe administration was gained.[4] A mortality rate of 16.9 per cent when compared with our preceding five years experience (46.6 per cent) appeared promising and justified further study.

Subsequent studies of blood and plasma viscosity with a Brookfield cone-plate viscometer, plasma proteins measured by paper electrophoresis, and blood hematocrits were performed in an effort to gain further knowledge of the nature of the sludging phenomenon and its response to treatment. It was also hoped that a more objective means of measurement could be found than the unreliable visual picture of sludging. The results have been reported.[7] Consistent changes in plasma proteins were recorded, but their probable relationship to the sludging phenomenon is as yet unproved. Likewise, the striking but varied changes in whole blood viscosity lend themselves easily to interpretation, but these studies need to be repeated with more refined instrumentation.

At this point, it was deemed necessary to establish the value, as measured by patient survival, of LMDx infusion in acute myocardial infarction. The results

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of the consequent randomized study constitute the essence of this report.

Method

1 Patients were included in the study if a positive or strongly presumptive diagnosis of acute myocardial infarction of less than 24 hours duration was made. Cases were dropped if the presumptive diagnosis was not proved.

2 Patients were randomized into Group A and Group B on the basis of a predetermined digit in their hospital registration number (odd or even)

3 All patients were treated on the Cardiovascular Service by one of the authors and received the standard treatment with oxygen, rest sedation anticoagulation with coumarin products, and digitalis, vasopressors, or antiarrhythmic agents as indicated

4. Group A (controls) received in addition 500 c.c. of 5 per cent glucose in distilled water intravenously in the first 4 hours then 500 c.c. every 8 hours for an additional 72 hours. A liquid diet was given for the first 3 to 4 days.

5 Group B (treated) received 500 c.c. of 10 per cent LMDx in 5 per cent glucose in the first 4 hours intravenously followed by 500 c.c. every 8 hours for 72 hours. A liquid diet was given for the first 3 to 4 days. The LMDx infusion was reduced and substitute hydration with 5 per cent glucose was given whenever observations of the urine volume and specific gravity indicated reduced renal excretion of dextran (Urine volume less than 250 c.c. for 6 hours urine specific gravity 1 065 or greater)

6 Excluded from the study were those patients who were obviously dying Patients in either group who died within less than 4 hours of the beginning of infusions were excluded on the basis that they had not (in the LMDx cases) received an adequate initial dose. Patients were also removed from the study when the presumptive diagnosis could not be proved Several patients were not included in the study because of the failure of the clinician to make a presumptive or positive diagnosis to justify inclusion into the study until the illness was more than 24 hours old

7 The end point of this study was death during hospitalization for the acute illness or in the first 21 days of the illness, whichever was the longer

Results

This study extended from July 1 1963 through Feb 28 1967 excluding a two-month period from April 1 1965 to June 1 1965 when the entire study was temporarily discontinued because of the unavailability of LMDx. A total of 13 infarctions were treated in this latter period and will not be included in any of the subsequent considerations. In the 42 month period of the study a total of 136 cases of myocardial infarction initially or subsequently proved to have been hospitalized within 24 hours of the onset of the illness were recorded This included all infarctions admitted to this hospital. By the randomization system 75 had glucose numbers (A) and 61 had dextran numbers (B) Six patients (3 in each group) were excluded because they were dying at the time of admission or died suddenly after admission before a positive or presumptive diagnosis had been made four patients were removed from the study because of death in less than 4 hours (3 in A, 1 in B) 16 patients, all of whom lived were not included in the study because of failure to make the diagnosis within the 24 hour period (4 in A 12 in B) There remained 65 cases in Group A and 45 cases in Group B In this period 6 cases were started on the study with a presumptive diagnosis of acute infarction, but dropped when the diagnosis could not be proved (5 in A 1 in B)

The two groups appeared comparable, as shown in Table I

COMPLICATIONS No known complications from the LMDx occurred. One patient developed a flush reaction which has been seen in our practice one time as the result of LMDx infusion. In this case it was thought due to sensitivity to a sulfa drug. Later in the study the same patient returned with a second infarction and received LMDx from the same lot without incident.

All cases in the series were analyzed to ascertain the incidence of common complications of acute infarction.

Cardiac decompensation. Decompensation in Table II is defined as the clinical state of the patient, excluding arrhythmias, which in the judgement of the cardiologist required digitalis therapy. The bases listed are those recorded in the clinical records.

Arrhythmia. Arrhythmia in Table III is defined as a documented rhythm change which in the judgement of the cardiologist justified specific therapy. The nature of the rhythm changes are as recorded in the clinical records.

Shock. In Table IV, shock is defined as a low level of recorded blood pressure which in the judgement of the clinician required vasopressor therapy. In all cases the mean blood pressure was < 75 mm. The cases are divided between the terminal or unresponsive shock and the shock which responded to therapy, which in all cases was either levarterenol or metaraminol.

Because of the importance of adequate hydration and urine volume, especially in cases receiving LMDx, records of intake

Table I

Group	N	Mean age	Known diabetes	Known past infarction	Past known hypertension under treatment	Per cent female	Location of infarction: Anterior		Posterior or posterolateral		Lateral		Subendocardial	
							N	Per cent	N	Per cent	No.	Per cent	No.	Per cent
A	65	61.9	4	8	6	20.0	28	43.1	30	46.2	1	1.5	6	9.2
B	45	60.6	3	10	4	22.2	18	40.0	20	44.4	6	13.3	1	2.2

*See text for explanation.

Table II

Group	Failure (total)		Increasing râles	Increasing râles plus gallop rhythm	Gallop rhythm	Venous pressure > (15 cm.)	Undet.
	No.	Per cent					
A (65 cases)	30	46.1	12	5	8	1	4
B (45 cases)	18	40	7	3	5	0	3

Table III

Group	Total		Occasional ventricular premature beat	Nodal or atrial arrhythmias	1 1 block	Sinus bradycardia < 50	Frequent ventricular premature beats	Ventricular tachycardia
	No.	Per cent						
A (65)	36	40	13	3	1	2	5	2
B (45)	19	42	9	3	2	0	3	2

and output were kept. In Tables V through VIII totals are for the calendar day of the illness. By presuming a random distribution of admission times throughout the 24 hour day the mean time for the first day would equal 12 hours only A total of 61 records in Group A and 42 in Group B were analyzed as shown in Table V

Of some speculative interest is the comparison of the differences between the total intake and output in the two groups (Table VI)

In the group receiving LMDx 17 required reduction in input because of evidence of impaired excretion. This number included 4 of the 6 deaths. The degree of reduction in the LMDx infusion for which substitute infusion with 5 per cent glucose is shown in Table VII

In analyzing the figures in Table VIII presuming that there is no difference between the groups the mortality rate would be 27 in 110 cases or 24.5 per cent. By the method of comparing differences between proportions, the probability of the difference in mortality rate (32.3 per cent − 13.3 per cent or 19 0 per cent) occurring by chance alone would be 2.28 standard deviations. This difference is considered significant (p = < 0 03)

The probability that death in patients receiving a new form of therapy might have been caused by that therapy must be considered In our clinical experience within this group such a relationship was not clearly evident. Reports of the six patients who received LMDx and died are summarized below

Case 1 A 69-year-old Caucasian man was admitted on Oct. 26, 1963, with severe substernal pain of one hour duration, radiating into the left arm H had sustained an acute posterior infarction in 1959 The ECG showed an acute anteroseptal

Table IV

Group	*Total*		*Terminal shock*	*Nonterminal shock*
	N	*Per cent*		
A (65 cases)	11	16 9	4	7
B (45 cases)	4	8 9	1	3

Table V

Group	*Day 1* (ml.)	*Day 2* (ml.)	*Day 3* (ml.)	*Day 4* (ml.)
Intake				
A				
Oral (mean)	385	930	1,230	1,220
Intravenous (mean)	1,000	1,500	1,500	1,000
Total (mean)	1,385	2,430	2,730	2,220
Range (oral)	0–1,270	110–3,070	130–3,330	230–3,[illegible]50
B				
Oral (mean)	700	1,220	1,315	1,385
Intravenous (mean)	1,000	1,500	1,300	1,000
Total (mean)	1,700	2,720	2,815	2,385
Range (oral)	0–1,875	90–3,400	120–3,610	140–3,115
Urine output				
A				
Mean	580	1,730	2,145	1,815
Range	0–2,680	300–5,695	200–6,550	350–4,600
B				
Mean	1,100	1,960	1,750	1,820
Range	0–3,450	310–5,270	395–3,600	435–4,265

Table VI

Group	Total intake 3½ days (ml)	Urine total output 3½ days (ml)	Difference (ml)
A	8 765	6 270	2 495
B	9 620	6 730	2 890

Table VII

No. of bottles reduced	No. of cases
1	3
2	2
3	6
4	2
5	2
6	1
8	1

Table VIII

Group	No. of cases	No. of deaths	Mortality rate (%)
A	65	21	32 3
B	45	6	13 3

infarction. Hypotension and heart failure were present for which digitalis and intravenous vasopressors were given. He received the first two bottles of LMDx and was then switched to 5 per cent glucose because of a low urine volume. An initial satisfactory response to vasopressors could not be maintained and he died in profound shock 26 hours after admission.

Case 2 A 74-year-old Caucasian man was admitted on Nov. 26 1963 for severe retrosternal pain radiating into the left arm. He had been hospitalized two weeks earlier with an acute anterior infarction and had left the hospital without medical consent on the tenth day. The ECG showed an acute lateral extension of his infarction. He received two bottles of LMDx. Vital signs and urine output remained satisfactory until his sudden death 12 hours after admission. Postmortem examination confirmed the recent anterior infarction with acute extension.

Case 3 A 64 year-old Caucasian man was admitted on May 28, 1964 because of severe precordial pain radiating down the left arm with extreme weakness, dyspnea, and drenching sweats. He gave a past history of atrial fibrillation and chronic myocardial ischemia for which he was taking digitalis, plus extensive malignant disease of the mouth and cervical lymph nodes, for which he was receiving irradiation therapy. The ECG showed a massive posterolateral infarction with marked sinus bradycardia and second-degree heart block. Râles in the lungs and a gallop rhythm were present. He received the initial six bottles of LMDx and then was switched to 5 per cent glucose because of reduced urine volume. The course was complicated by abdominal pain and distension with an amylase of 720. His condition remained reasonably stable except for a persistent gallop rhythm until he died suddenly on June 1 1964 on the fifth day of his illness.

Case 4 A 69-year-old woman was admitted on Jan. 18, 1965 because of precordial pain, nausea, and syncope of five hours duration. A long history of severe chronic asthma was recorded. Pallor, sweating, and a gallop rhythm were observed. ECG showed a posterior infarction. She received digitalis and six bottles of LMDx interspersed with 4 bottles of 5 per cent glucose because of low urine volume. On the fourth hospital day moderately severe wheezing began, incompletely controlled by isoproterenol and aminophylline. On the twelfth hospital day she developed severe precordial pain and died. Postmortem examination showed thrombosis of the right coronary artery with posterior infarction plus a recent thrombosis of the circumflex branch of the left coronary artery with an acute lateral infarction.

Case 5 A 57 year-old Caucasian man was admitted on June 1 1966 with severe precordial pain of three hours duration. ECG showed an acute anterior infarction. He received only two bottles of LMDx and the remainder 5 per cent glucose because of low urine volume. The early course was complicated by recurrent ventricular tachycardia requiring cardioversion, heart failure requiring digitalis and hypotension reasonably responsive to vasopressors. He remained severely ill during his hospital course and developed ventricular fibrillation unresponsive to attempts at cardioversion on the tenth day of his illness.

Case 6 A 48-year-old obese diabetic woman was admitted on Jan. 9 1967 with a three-hour history of severe precordial pain syncope dyspnea, and diaphoresis. An anterolateral infarction was read on ECG. She received one bottle of LMDx during which time her urine output was adequate and her general condition satisfactory. Six hours after admission she abruptly developed tachycardia, severe dyspnea, hypotension, and pulmonary edema and died in 20 minutes in spite of emergency treatment for heart failure.

Discussion

Randomization by the registration number was chosen initially because of the need in many cases to proceed on the basis of a presumptive diagnosis, even though some of the cases would eventually be removed from the study. For each individual admitted with a myocardial infarction

there should be a 50 per cent chance of his falling into either group In hindsight, if the number of cases required to achieve significant results could have been predicted randomization by a sealed-envelope system would have been better Not only would this system probably have produced more equal groups, but it would have eliminated what appears to have been a greater inclination by the clinician to make a presumptive diagnosis on the basis of suggestive findings alone when the number was a control number than when it meant giving LMDx. There was no sign of a disinclination on the part of the clinician to give LMDx to the very ill patients. The tabulation of all potential cases which did not enter the study however does not appear to have biased the results in favor of the treated group. In future studies, the problem presented by the frequent need to proceed on a presumptive diagnosis in order to initiate therapy within the 24 hour period can best be solved by randomization with the sealed-envelope system and returning the used number when a presumptive diagnosis is not proved

In this study there was no significant difference between the two groups in the occurrence of heart failure or arrhythmias. Therefore, the LMDx did not appear to benefit the patients by reducing these complications. The difference in the incidence of shock is greater but not statistically significant (1.2 standard deviations)

The difference in the mortality rate between the control and the treated groups is in contrast with the findings of Borchgrevink and Enger[4] who could document no benefit from LMDx infusions. It should be noted however that Borchgrevink gave LMDx intermittently in limited amounts. The two studies are therefore not comparable. Borchgrevink had rejected the treatment program used in our study after a short pilot study had resulted in a very high mortality rate. His observations in the pilot group underline a fact which we have found true that LMDx cannot be given by *continuous* infusion without an understanding of the hazards of reduced excretion A total of 17 of our 45 treated cases required modifications in the program of regular infusions. Failure to limit LMDx in these cases might have increased the mortality rate above the observed figure. Herein lies the greatest problem in this form of therapy The LMDx in the 10 per cent solution is an osmotically active agent and consequently has a plasma-expanding effect (1 Gm. of dextran will hold in circulation about 20 c.c. of water) Overexpansion of the plasma volume in patients with severely and acutely injured hearts is dangerous.

The per cent concentration of dextran in the blood can be measured by the Wallenius method[19] Unfortunately because of its osmotic activity the concentration is not an accurate reflection of the total circulating dextran mass which determines the magnitude of plasma expansion. Consequently measurements of serum concentration by any method cannot serve as a reliable means for monitoring Serial measurements of the circulating blood volume would be needed every few hours to be of value The best indication of overdosage is the development of an abnormal central venous pressure (> 15 cm.) Ideally this point should not be reached Neither should LMDx be given in the presence of pulmonary edema. In no instance in the total 110 cases of acute infarction (including both the preliminary study and this study) was an initially normal venous pressure raised to over 15 cm. by the first 500 c.c of LMDx given in the initial four hours. With normal renal excretion this level of increase can be maintained by the continuing infusion of 500 c.c. every eight hours. Subnormal excretion with continuing maintenance infusion must result in further increase in the plasma volume. The problem is to identify inadequate renal excretion and reduce maintenance infusion accordingly In the preliminary study the syndrome of the clinically ill patient, scanty oral fluid intake low urine volume, and high urine specific gravity invariably preceded the appearance of an elevated venous pressure and frank pulmonary edema if infusion rate was not reduced

From this earlier experience the program of substituting 5 per cent glucose in distilled water for the LMDx when the urine volume fell below 250 c.c for 8 hours or the

urine specific gravity rose to >1 065 was adopted If these findings were no longer present after the following six hours the LMDx infusion was resumed Following these guidelines the venous pressure never exceeded 15 cm in the 45 cases in this study A state of renal dysfunction with isosthenuria will invalidate these criteria since it may permit an acceptable urine volume without a high urine concentration No cases of isosthenuria were noted in this study but three were observed in the preliminary study A low but adequate urine volume with a specific gravity consistently <1 030 suggests inability of the kidneys to concentrate urine and requires a reduction in the maintenance infusion. The need to reduce the infusions in 17 of 45 cases is appreciable, and implies that greater safety might be assured by a less rapid infusion program

The data on voluntary fluid intake show that oral hydration is remarkably poor in these acutely ill patients and tends to reflect the severity of the illness. The total oral intake in Group B was slightly greater than Group A (4 620 vs. 3 765 ml) Whether this is due to an increased thirst in patients receiving LMDx, a generally improved state of the patient or chance is unknown The difference between intake and output over the 3½ day infusion period was 395 ml greater in Group B than Group A and might possibly reflect the increase in plasma volume Such an increase in plasma volume would correlate closely with the mean fall in venous blood hematocrit (42→39 per cent)

Severe oliguria was observed in both groups. *In Group B it was associated with a highly viscid urine* (specific gravity recorded as high as 1 095) Our observations do not convict or exonerate the LMDx as a factor in the oliguria. Infusion of LMDx is not advised in the anuric patient

The administration of LMDx to patients with acute myocardial infarction has been shown beneficial at the level of statistical significance All surviving patients are being followed to determine long term mortality rate figures. Whether the benefit has been due to a reduction in cellular aggregation with improved microcirculation a reduction in whole blood viscosity with decrease in cardiac work or the beneficial effect on shock from increased plasma volume is not delineated from these studies. In view of these good results, further study deserves a high priority being cognizant of the fact that the administration of LMDx to these severely ill patients must not be over simplified

Summary

A total of 110 cases of acute myocardial infarction were randomized into two groups. Group A received standard therapy plus 5 per cent glucose in water 500 c.c. in the first four hours, then 500 c.c. every eight hours for 72 hours. Group B received standard therapy plus 10 per cent LMDx in 5 per cent glucose 500 c.c. in the first four hours, then 500 c c. every eight hours for 72 hours A total of 65 cases fell into Group A and 45 cases in Group B There were no complications from the LMDx therapy The mortality rate in Group A was 32 3 per cent and in Group B was 13 3 per cent. The probability of this variance occurring by chance is less than 3 per cent. The problems associated with dosage control have been presented

REFERENCES

1 Bloch, E. H I vivo microscopic observations of the circulating blood in acute myocardial infarction, Am. J M Sc 229:280 1955
2 Gelin, L. E. Studies in anemia of injury Acta chir scandinav Suppl. 210.1 1956.
3. Long D M Myer M W Brown, E. B and Lillehei, C W Myocardial necrosis and electrocardiographic changes related to microcirculatory abnormalities, Am. J Cardiol. 10:695 1962.
4 Langsjoen P H Falconer H S Sanchez, S. A. and Lynch, D J Observations in treatment of acute myocardial infarction with low molecular dextran, Angiology 14:465 1963
5 Langsjoen, P H.: Observations in the excretion of low molecular dextran, Angiology 16 148 1965.
6. Langsjoen, P H Blood viscosity changes in acute myocardial infarction, Postgrad. Med 39:12, 1966.
7 Langsjoen, P H and Inmon T W Rheologic changes in myocardial infarctions, AM. HEART J 73:430, 1967
8. Borchgrevink, C. F and Enger F : Low molecular-weight dextran in acute myocardial infarction Brit. M J 2:1235 1966.
9 Hint, H.: The relationship between the molecular weight of dextran and its effects, Symposia on Rheomacrodex, 1:2, Report of London and Cardiff meetings, November 1961
10. Wallenius, G. Renal clearance of dextran measure of glomerular permeability Acta soc med. upsalien. Suppl. 4 1 1954

Treatment of idiopathic myocardial hypertrophy with thioguanosine

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Idiopathic myocardial hypertrophy (IMH) is a progressive, often fatal disease syndrome of young Negro men characterized by cardiomegaly and congestive heart failure. Since there is no specific diagnostic finding, the classification of myocardiopathies undoubtedly includes many separate clinical and pathologic entities. The cardiac lesion is that of nonspecific myocardial fibrosis. The clinical entity of IMH has been described by Burch and associates, Sanders and Ritts, Dye and co-workers,[3] and LeBauer and Bressler[4] and seems to include a distinct population.

There is some evidence to suggest that IMH may be an autoimmune disease. The onset often follows a respiratory infection and patients with IMH occasionally have other autoimmune disorders such as thyroiditis or hemolytic anemia. Antibodies to heart tissue have been found in many cardiac diseases. Bengmark and associates[7] have demonstrated myocardial cytotoxic antibodies in the plasma of patients with myocardopathies. Sanders[8] has demonstrated the presence of gamma globulin on heart muscle obtained from patients having IMH.

With the above information and the lack of any satisfactory therapy for patients unresponsive to digitalis or diuretics, we decided to explore the effects of an immunosuppressive agent, thioguanosine. The decision to use a compound of the thiopurine group was based on the marked improvement shown by a previous IMH patient after Imuran therapy. Thiopurines have been reported to have useful effects in a variety of disorders which may involve altered immunologic mechanisms in their pathogenesis.[9]

Methods

Eight patients were selected for this study from the population of the Durham VA Hospital. These patients were selected because they had an advanced disease which was stable or progressive despite careful medical management with cardiac glycosides and diuretics. Some of the clinical and laboratory findings are listed in Table I. Each patient had cardiomegaly, ventricular gallop, edema, and liver en-

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Table 1 Clinical laboratory and hemodynamic data from the 8 patients included in the present study

L u A	Age	Race	Laboratory studies						America heart classification			
			WBC	Hct.	A/G	BUN	LE prep	Serum iron	Before	After	Blood pressure	Fundus
47 218	50	W	3 600	42	2 8/3 5	18	Neg	—	III	II	110/80	0
49 038	46	N	4 750	39	3 3/4 6	18	Neg	128	II	II	156/110	I
51 670	48	N	4 700	40	2 2/5 2	18	Neg	144	II	I	130/80	I
2 374	48	N	3 000	40	2 2/4 1	23	Neg	150	III	II	130/80	I
36 647	45	N	4 500	41	3 7/3 3	25	Neg	210	III	II	130/90	0
44 764	43	N	4 800	45	4 5/2 8	17	—	—	III	II	120/80	0
1 699	48	W	6 700	43	3 0/3 4	23	Neg	107	III	III	130/80	
53 997	32	N	5 700	45	4 5/3 1	9	—	—	III	I	120/85	I

*WBC White blood count; Hct., hematocrit; A/G albumin/globulin ratio; BUN blood urea nitrogen; LE prep lupus erythematosus preparation.

largement. Each was briefly hospitalized at the beginning and again at the completion of the study in order to perform cardiac catheterization but remained ambulatory (except Patient 5) throughout the three-month period of observation. Patient 5 was referred for treatment by his attending physician after a six month period of bedrest which had failed to relieve severe congestive failure The interval between patient clinic visits was two weeks. Cardiac glycosides and diuretics were continued and appropriately adjusted during the course of the clinic trial

All patients were treated with an initial daily dose of 80 mg of thioguanosine Complete blood counts were repeated daily for the first several days and at two-week intervals thereafter The dosage of thioguanosine was reduced if the white blood count fell below 4 000 per cubic millimeter and the average maintenance dosage was 40 mg per day

Results

Eight patients were enrolled into this study and of these seven completed a three-month course of therapy Six of seven patients showed an improvement in cardiac output (Table II) and six of the original eight patients had significant improvement in therapeutic classification (New York Functional Classification) One patient (Patient 3) was removed from the study for failure to keep his clinic appointments after he felt improved The one patient who completed the trial but was not improved symptomatically was Patient 7 His cardiac output had increased by the end of the study despite the accumulation of 40 pounds of edema during the three-month trial Patient 5 had been at bed rest for six months prior to the study and became increasingly dyspneic at rest despite maximal therapy One month after the onset of thioguanosine he developed a left femoral artery embolism which was successfully removed. He improved rapidly thereafter and became fully ambulatory without dyspnea His heart size decreased to normal and the hemodynamic data showed an increase in cardiac output and a decrease in end-diastolic pressures. Thioguanosine therapy was discontinued after two months, and his improvement has been maintained over the ensuing six months of observation Serum electrophoresis was normal and remained unchanged during the study in all patients studied

Discussion

There were two major problem in designing a clinical trial using IMH patients (1) difficulty in establishing an unequivocal diagnosis, and (2) difficulty in establishing reliable objective parameters of responsiveness. In the absence of

Table II *Chest x rays and cardiac catheterization before and after therapy with thioguanosine*

ECG*	Chest film		Catheterization			
	Before‡	*After*	*Before rest*	*After rest*	*Before exercise*	*After exercise*
LVH LAE, LBBB	18.29	15.29	P.A. 23/12 (M) 13 C.O 4,018 ml./min.	28/12 8 4,510	31/12 17 4,230	29/6 17 4,820
LVH DE	19.29	18.29	P.A 26/18 (M) 19 C.O 3 663	33/9 15 3,800	36/14 24 3,827	45/14 21 4,000
LVH	16 5.28	13 8.28 5†	P.A. 32/12 (M) 23 C.O. 3,800			
LVH DE	18.28	15.28	P.A. 28/12 (M) 20 C.O 1 740	29/6 17 2,600	31/12 15 2,830	42/15 20 4,670
LAE, RAE	18.31	14 5.29 5	P A 28/12 (M) 10 C O 2,830	29/6 17 4,620	32/14 12 3,250	37/8 20 4,820
LAE, LVH	15.31	14 2.31	P.A 23/9 (M) 11 C.O 3 085	18/5 10 3 712	31/13 24 4,694	26/8 11 5,991
LVH	19 8 34	22.35	P A 54/24 (M) 35 C.O 4 769	45/20 31 6,656	62/41 52 5,259	60/31 41 6,097
LVH DE	19.29	19 29	P.A. 33/16 (M) 29 C.O 4,027	30/14 29 3 186	35/18 30 4,500	38/14 30 4,000

*LVH, Left ventricular hypertrophy; LBBB, left bundle branch block, LAE, left atrial enlargement RAE, right atrial enlargement DE, digitalis effect
†X-ray made ten days after the onset of treatment.
‡Before refers to determinations prior to treatment

known pathognomonic criteria for the diagnosis of IMH it was essential to attempt to rule out other types of myocardiopathies. It was often difficult to exclude hypertensive cardiovascular disease since IMH patients exhibit a narrowed pulse pressure with diastolic readings of about 100 mm. Hg and have often been told that they had hypertension. In such cases, the presence of normal fundi was established as a criterion for inclusion in this study as it would be distinctly unusual for hypertensive vascular disease to cause advanced cardiomegaly without retinopathy To minimize the possibility of confusion with arteriosclerotic heart disease (ASHD) patients over 50 years of age or those with a history of angina were excluded. Six patients had negative LE preparations and a normal serum iron and normal serum electrophoresis.

The problem of evaluating responsiveness was primarily due to the spontaneous fluctuations in the disease which result in periods of heart failure followed by periods of relative improvement. This difficulty was, however obviated in Patients 1 to 4 whose clinical course was quite

stable for many months prior to treatment. Since prolonged bed rest may cause a decrease in heart size and clinical improvement in some patients,[1] an attempt was made to select patients who would be ambulatory during the course of therapy. It is also necessary to recognize the fact that this was a preliminary nonrandomized study and a "placebo effect" and the quality of supportive therapy during the trial period could have influenced responsiveness to some degree. The status of the disease, however, may be determined with reasonable accuracy by changes in performance, cardiac size, and hemodynamic parameters, particularly cardiac output and diastolic filling pressures.

Despite the difficulties of interpretation mentioned above, it is apparent that six of the eight patients were distinctly improved during the trial period. These findings are intriguing in a disease in which the prognosis is poor and in which there is no known satisfactory treatment. We feel that these results warrant the performance of a randomized clinical trial to test the validity of these interpretations. Further observations are also needed to determine the effects of therapy on cardiac antibodies.

Summary

Thioguanosine was given to eight patients with idiopathic myocardial hypertrophy. The drug was well tolerated. Six of the seven patients who completed the trial had subjective and objective indications of improvement.

REFERENCES

1. Burch, G. E., Walsh, J. J., and Black, W. C.: Value of prolonged bed rest in management of cardiomegaly, J. A. M. A. 183:81, 1963.
2. Sanders, V., and Ritts, R. E., Jr.: J.A.M.A. 191:59, 1965.
3. Dye, C. L., Rosenbaum, D., Lowe, J. C., Behnke, R. H., and Genovese, P. D.: Primary myocardial disease. I. Clinical features, Ann. Int. Med. 58:426, 1963.
4. LeBauer, J., and Brewler, R.: Idiopathic myocardial hypertrophy, South. M. J. 55:694, 1962.
5. Sanders, V.: Arch. Int. Med. 112:661, 1963.
6. Fialkow, P. J., Fudenberg, H., and Epstein, W. V.: "Acquired" antibody hemolytic anemia and familial aberrations in gamma globulins, Am. J. Med. 36:188, 1964.
7. Bergmark, S., Frisen, L., and Helander, E.: Acta allergol. 18:179, 1963.
8. Corley, C. C., Jr., Lessner, H. E., and Larsen, W. E.: Am. J. Med. 41:404, 1966.
9. Rundles, R. W., Laszlo, J., Itoga, T., Hobson, J. B., and Garrison, F. E., Jr.: Cancer Chemotherap. Rep. 14:99, 1961.

Serious and fatal complications of catheterization and angiocardiography in infants and children

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The complications of selective angiocardiography may be divided into three areas (Table I): (1) those related to the hazards of cardiac catheterization per se, (2) those due to the mechanics of rapidly injecting a large volume of fluid into the heart and/or great vessels, and (3) those due to the hyperosmolarity of the contrast medium which produces physiologic and pathologic changes.[1] A general classification of the complications encountered is shown in Table I.

The risk of such complications is much higher in infants because of (1) the smaller size and thinner walls of vessels and cardiac chambers, (2) the lesser mass of circulating blood and organs of impact, and (3) the higher frequency of severe congenital heart disease with attendant problems of cyanosis, heart failure, and disturbed cardiopulmonary dynamics.

This paper will report and discuss our morbidity and mortality experience resulting from 1,104 consecutive cardiac catheterization and angiocardiographic procedures on the pediatric cardiology service.

Materials and methods

All catheterization and angiocardiographic data with particular emphasis on complications were punched onto IBM cards for retrieval and analysis (Fig. 1). This series began with our first patients in 1959 and ended on June 30, 1967.

All patients who died following cardiac catheterization and/or angiocardiography were counted as a catheterization death if the procedure was considered to be a factor in the child's demise. The elapsed time since catheterization was not the sole factor in this decision. In six cases a causal relationship between the procedure and subsequent death appeared unlikely and they were not counted as fatalities.

Two male infants, ages seven days and one month, with complete transposition of the great vessels, underwent angiocardiography without apparent ill effect. Both died after seven days and three days, respectively, of massive infarction of the bowel. While this might have been related to the contrast medium injection throm

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Table I. Complications of catheterization and angiocardiography

Complications related to insertion and passage of the catheter
- Infection
- Perforation of vessel or heart[3]
- Knotting or breakage of catheter
- Dislodgement of prior existing thrombus
- Arrhythmias
  - Supraventricular tachycardia
  - Cardiac arrest: either asystole or ventricular fibrillation
- Electric shock[4] producing arrhythmias
- Air embolism
- Hypothermia
- Acidosis

Complications of rapid injection
- Mechanical
  - Dislodgement of thrombi
  - Extrasystoles
  - Extravasation into myocardium
  - Rupture of coronary sinus
- Chemical
  - Thrombosis
  - Cerebral edema
  - Cardiorespiratory collapse[16]

bosis occurs spontaneously in patients with cyanotic congenital heart disease.

A one-year-old boy underwent aortography and angiocardiography and on the next day dislodged his endotracheal tube. Respiratory distress and cardiac arrest ensued before the tube could be replaced.

Three additional cyanotic infants were *also not considered to have died as a direct* result of catheterization. A one-day-old cyanotic infant with pulmonary atresia had a catheter placed into the right atrium preparatory to an angiocardiogram. The dose of digitalis due at this time was administered at 10 times the intended dose but this error was not recognized until atrioventricular dissociation occurred two hours later. A selective right ventricular angiocardiogram was performed in a one-day-old infant with aortic atresia. He tolerated this procedure well but over the next 24 hours, his condition became poor and he died approximately 26 hours after the procedure. A 10-month-old girl began having spells of paroxysmal hyperpnea followed by extreme cyanosis at six months of age. Angiography revealed a severe form of tetralogy of Fallot with valvar pulmonic atresia. Three days after the procedure, she had a severe cyanotic episode and died.

In five cases there was a tenuous relationship between the procedure and death, but these were counted as such for purposes of analysis.

Case reports

Case 1. A 5-month-old boy with pulmonic valvar stenosis and right-to-left shunt at the atrial level became severely ill following catheterization and angiocardiography, after which a surgical attempt was made to relieve his pulmonic stenosis. The child died during the operation. This was counted as a catheterization death since his degree of cardiopulmonary distress increased enormously during and following catheterization.

Case 2. A 3-day-old boy entered the hospital in severe congestive heart failure. A patent ductus arteriosus was suspected because of the location of the systolic murmur and bounding pulses. In spite of his critical condition, it was felt that his only chance for survival was to prove the diagnosis. As further evidence of the severity of his condition, the mean left atrial pressure was 28 mm. Hg. He died almost immediately after an angiocardiogram.

Case 3. A diagnosis of aortic atresia had already been established in a 21-day-old girl by a previous retrograde aortogram. An attempt was made to obtain hemodynamic data by right heart catheterization to see if a Blalock-Hanlon procedure would be feasible. She died during the course of this catheterization.

Case 4. A 2-year-old girl, with a history of syncopal attacks, had a diagnosis of primary pulmonary hypertension established at an uneventful right heart catheterization. She returned home and died there on the third postcatheterization day during such a syncopal attack.

Case 5. In spite of an obviously critical condition and a clinical diagnosis of persistent truncus arteriosus, an 8-day-old girl had a thoracic aortogram performed. She died 3 hours after the procedure.

Using these stringent criteria, we have had a total of 27 deaths following catheterization and/or angiocardiography. All the deaths except three occurred in children under one year of age. These older patients were (1) a 2-year-old child with a complete atrioventricular canal, a reversed central arterial shunt, and a posteroanterior (PA) pressure of 155/90, (2) a 6-year-old child with a complete atrioventricular canal who died of air embolism, and (3) the child described above in Case 4.

Results

Table II lists our fatalities by year of occurrence. In the last $1\frac{1}{2}$ years the mor

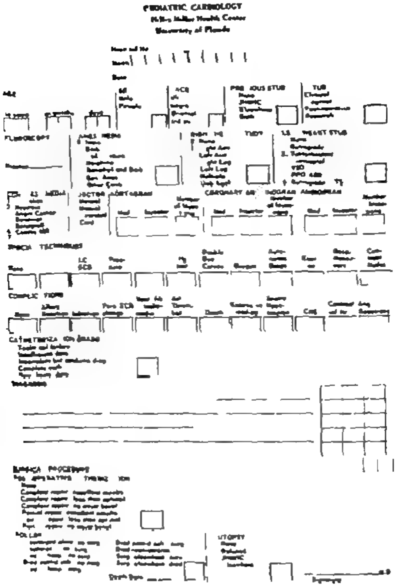

Fig. 1. This card is initially filled out at catheterization and then corrected when the final typed catheterization note is signed. This helps ensure that late complications will be coded. The data from this card are then key punched onto an 80 column IBM card.

tality rate has been 1.3 per cent compared to 2.9 per cent prior to that time.

Mortality rates were highest for the younger patients (Table III). Therefore our analysis concentrated on patients under six months of age since it was felt that this would more likely point out any adverse effects of the procedures.

General anesthesia was not used in any infant under one year of age. No adverse effect of sedation on mortality rate was noted. If anything, patients who were sedated actually had a slightly lower mortality rate of 5.5 per cent as against 9.1 per cent for those with no sedation. This is most likely due to our tendency to omit sedation in severely cyanotic or acutely ill infants. Thus, patients who were sedated were generally better risk cases.

Analysis of mortality rates by the number of injections of contrast medium utilized in children under six months of age is given in Table IV. The highest mortality

Table II. Cardiac catheterization and angiocardiographic mortality by year

Year	Procedures	Fatalities	Rate ( )
1959	7	0	—
1960	51	1	2.0
1961	93	4	4.2
1962	123	0	—
1963	151	5	3.3
1964	171	5	2.9
1965	189	8	4.2
1966	200	2	1.0
To July 1, 1967	119	2	1.7
	1,104	27	2.4

Table III. Cardiac catheterization and angiocardiographic mortality by age

Age	Procedures	Fatalities	Rate ( )
Under 1 month	71	7	9.8
1 to 5 months	204	15	7.4
6 to 11 months	81	2	2.5
Subtotal under 1 year	356	24	6.7
1 to 5 years	340	2	0.6
6 to 10 years	259	1	0.4
11 to 15 years	135	0	0
Over 15 years	14	0	0
Subtotal over 1 year	748	3	0.4
Total	1,104	27	2.4

Table IV. Mortality by number of injections in patients 0 to 6 months of age

Injection	Procedures	Deaths	Rate ( )
None	36	7	19.5
1	119	8	6.7
2	8	4	5.1
3	29	2	6.9
4 or more	13	1	7.7
Totals	275	22	8.0

rates occurred in patients who underwent catheterization alone. However, angiocardiography was planned for four of these seven infants and would have been carried out if these infants had not become severely ill during the catheterization. There was no significant increase in mortality rates after the first injection. Thus it would appear that if an infant can tolerate one injection, one or two additional injections carry little additional risk.

Several significant correlations were found with data obtained early in the catheterization and prior to angiocardiography. All except four of the patients who died had arterial desaturation ranging from 35 to 91 per cent. A total of 22 of the 24 measured right ventricular end-diastolic pressures and nine of 17 left ventricular end-diastolic pressures were elevated. Right ventricular end-diastolic pressures averaged 15.6 mm. Hg (range 6 to 30) and left ventricular end-diastolic pressures averaged 13.5 mm. Hg (range 4 to 28). Finally, in all 22 instances where measured, the children who died had either pulmonary or right ventricular hypertension (ranging from 53 to 126 per cent of systemic). Not surprisingly, the most striking correlation of mortality rates was with severity of the cardiac pathophysiology.

Discussion

We have chosen to classify complications into two groups. First, those related to the insertion and passage of the catheter itself and second, those due to the rapid injection of a bolus of contrast medium (Table I).

Introduction of the catheter of necessity involves violating the integrity of the skin and carries a risk of introducing infectious agents. We have had only one serious local infection. This occurred in a four-month-old male infant with complete transposition of the great vessels. An infection of the cutdown site in the groin delayed operation and he died seven days after the catheterization. Bacterial endocarditis following catheterizations is fortunately rare and we have not seen this complication in our group of patients. None of our patients are given prophy-

Fig 2 Perforation of the aorta by guide wire This 0.025 inch diameter ire was inserted into PE90 polyethylene catheter to visualize and guide the catheter This 3-month-old boy died 3 hours later Necropsy revealed pulmonary tresia nd intact ventricular septum

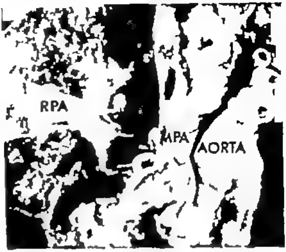

Fig 3 This 5-month-old girl had enous catheter inserted i t the SVC and an ngiocardiogram per formed using only hand-generated pressure on syringe She died within 10 minutes of massive pulmonary embolus (arrow). Necropsy revealed that the entire SVC jugular stem nd parts of the right trium were filled with thrombus Previous meningit had caused thrombosis of the jugular eins with subsequent propagation into the SVC nd right trium.

lactic antibiotics for catheterization or angiocardiographic procedures.

The relatively thin vessel walls and small cardiac structures in infants increase the possibility of perforation by a stiff catheter In one three month-old child a polyethylene catheter was introduced into the right brachial artery but could not be passed into the ascending aorta. A guide wire was inserted to aid in visualization and placement of the catheter When this proved unsuccessful the catheter and wire were removed and t was noted that the guide wire had perforated the catheter wall Shortly after this, the infant's blood pressure dropped rapidly and he died in spite of repeated intravenous blood transfusions. At necropsy a small tear in the aorta was found (Fig 2)

Perforation of a vessel or of the heart may be recognized by the abnormal position of the catheter failure to withdraw blood or a change in the pressure tracing If a 5 French or smaller catheter penetrates the aortic arch Dr Robert Miller of Chicago recommend that a needle be placed in the pericardial space after which the catheter can be withdrawn back into the aorta to monitor pressure. If the cardiac silhouette enlarges or the pressure drops blood is withdrawn from the pericardiac sac and returned intravenously This process is continued until fluid stops accumulating and the pressure is stable The puncture site will usually close spontaneously If the catheter is 6F or larger it should be left in place and provisions made for closing the perforation at thoracotomy Perforations of the atria especiall the left atrium are not as predictable while ventricular perforations will usually seal spontaneously without serious sequelae

Knotting or breaking of a catheter Seldinger wire or transeptal needle tip have all been reported These incidents are particularly unfortunate since little can be done to prevent them after the catheter is inserted All such equipment should be inspected prior to use and discarded if there are any indications of cracking or other damage In our two experiences with catheter breakage both catheters were of the NIH type In each instance the end section broke on withdrawal of th catheter fortunatel the broken piece was in a peripheral vein and was easily removed with a forceps.

Transient arrhythmias such as prema

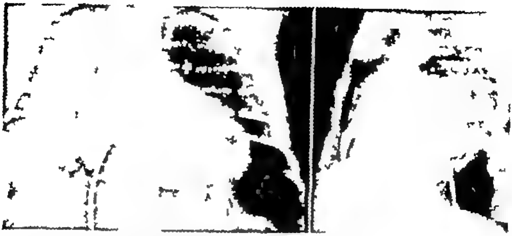

Fig. 4. Myocardial infiltration of the right ventricle in a 7-day-old boy with complete transposition of the great vessels. In the AP view the No. 5 50 cm. NIH catheter (closed tip with six side holes) appears to lie at the center of the right ventricle. The lateral view, however, shows that the catheter is caught in the trabeculations of the anterior wall.

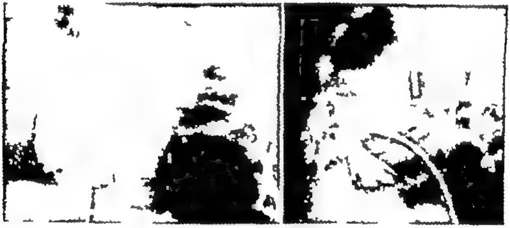

Fig. 5. Massive infiltration of the myocardium in a 3-day-old boy with situs solitus dextroversion and complete transposition of the great vessels. Abnormal cardiac positions increase the risk of injecting into the myocardium. The catheter utilized in this study was a No. 5 50 cm. Eppendorf catheter (closed tip with six side holes).

ture atrial or ventricular contractions occur so frequently that it is difficult to classify these as complications. Arrhythmias persisting for an hour or more occurred in 33 children. The dangers of current leakages and inadequate ground systems leading to ventricular fibrillation have been stressed in recent articles. Fortunately, early projects in our laboratory stressed the need for an adequate ground for research purposes and the laboratory was rewired. No instances of ventricular fibrillation in children were seen by either our group or Venables and Hiller[2] although Vlad and associates[8] reported four instances with two successful defibrillations. When cardiac arrest occurred, it has been due to ventricular asystole following a period of gradually decreasing heart rates. External cardiac massage and mouth-to-mouth breathing succeeded in reviving two of these infants.

Use of a pressure flush system where the fluid for clearing the catheter is under constant pressure of about 300 mm. Hg carries a danger of air embolism. We have had this occur on one occasion resulting in a fatal outcome. Since that time, we have devised an automatic alarm system to prevent its recurrence.

Fig. 4. A, Epicardial hematoma viewed 12 hours after infiltration of right ventricular myocardium with contrast media. (Hematoxylin and eosin; photograph reduced from ×75.) *B*, Acute necrosis and lysis of myocardial fibers surrounding myocardial sinusoid. Appearance 15 hours following injection of contrast media into right ventricle. (Hematoxylin and eosin; ×275.) *C*, Hemorrhage and peculiar pseudohyaline-like contracture of myocardial artery 15 hours following injection. This type of change was seen commonly throughout the right ventricular myocardium at this time. (Hematoxylin and eosin; ×175.) *D*, Late scar in right ventricular myocardium 6 weeks following injection. Some secondary hemorrhage is apparent in the lower portion of the field and the relationship of scar tissue to the sinusoidal and trabecular system is apparent. (Masson trichrome; ×8.)

Rapid injection of contrast medium resulted in the dislodgement of a preexisting thrombus and massive, fatal pulmonary embolus in one case (Fig. 3).

Extravasation of contrast medium into the myocardium tends to occur (1) in cases where there is marked hypertrophy of the myocardium and exaggeration of the trabecular pattern (Fig. 4) and (2) in cases where the anatomy of the heart is complex and the physician uncertain of the exact location of the catheter tip (Fig. 5). Some of the later consequences of myocardial infiltrations are shown in Fig. 6. Myocardial infiltrations occurred in 12 children, five of whom died shortly thereafter. This can best be avoided by using only catheters with a closed end and multiple side holes and preliminary injections of contrast medium with the use of manual pressure to check the exact location of the catheter tip.

Rupture of the coronary sinus has been reported[11] following rapid injection of contrast material. With the catheter high in the coronary sinus, it may impinge on the right ventricular (RV) wall and an RV pressure tracing may be recorded. The oxygen saturation of the coronary sinus is lower than that found elsewhere on right heart catheterization. The catheter usually passes closer to the diaphragm when entering the coronary sinus than when entering the tricuspid valve and withdrawal of the catheter a short distance results in a markedly different pressure

contour. Furthermore the catheter tip does not induce premature beats in this location. Although this complication has been reported by others, we have been fortunate enough to have avoided it.

Conclusions

A number of investigators have quoted extremely low or virtually nonexistent cardiac catheterization mortality rates.[13] However, Venables and Hiller[4] stated that in 5 per cent of 837 catheterizations performed in infants less than six months of age there were five deaths. Thus in this age group the mortality rate was 12 per cent. (Our comparable mortality rate in this age group was 8 per cent.) Lambert and associates[1] reported seven deaths following catheterization in 165 infants under one month of age. In a personal communication to the authors he stated that these occurred in a total of 73 catheterization procedures for a mortality rate of 9.6 per cent; this is virtually identical to the seven deaths in 73 procedures of the present series. Lambert goes on to say, "Since we submitted this article our incidence of death from this form of cardiac catheterization has risen from 10 to 15 per cent. I should mention that any patient who dies within 24 hours after cardiac investigation is considered a catheterization death."

The most significant correlations of death rate were with severity of the illness (Figs. 1 to 3). As a further proof of this statement, Table VI illustrates the spectrum of anomalies found in 26 infants who died during the same time period while awaiting cardiac catheterization. The entities in this group are similar to those found in patients who died following catheterization (Table V).

We are faced then with a dilemma, namely, that the highest risk of cardiac investigation occurs in those sick infants who for the most part will not survive unless successful operation can be performed. Adequate surgical management often requires prior cardiac catheterization and angiocardiography, both of which impose additional risks.

We have adopted several procedures as a result of our experience.

1. Infants under six months of age are seen by a pediatric cardiologist and a thoracic surgeon within 24 hours of admission. In many instances they are offered a 24 hour trial of medical management and stabilization prior to further procedures.

2. If the type of operation to be performed can be decided *without* further diagnostic procedures, these are omitted.

Table V. Influence of cardiac anatomy on mortality rates in children under 6 months of age, 1959 to 1967

Cardiac anomaly	*Procedures*	*Deaths*	*Rate (%)*
Cyanotic entities			
Aortic atresia	4	2	50
Complete transposition of great vessels	32	4	12
Severe tetralogy of Fallot	18	4	22
Other	56	1	2
Totals	110	11	10
Not or only mildly cyanotic			
Ventricular septal defect	57	6	11
Atrioventricular canal	15	1	7
Patent ductus arteriosus	11	1	9
Other	65	3	5
Totals	148	11	7

Table VI. Patients dying prior to cardiac investigation under 1 year of age, 1959 to 1967

Cardiac anomaly	*No. of patients*
Cyanotic	
Aortic atresia	4
Complete transposition of great vessels	4
Tetralogy of Fallot	2
Single ventricle	1
Truncus arteriosus	1
Tricuspid atresia	1
Total	13
Not and mildly cyanotic	
Ventricular septal defect	6
Patent ductus arteriosus	3
Pulmonic stenosis	1
Endocardial fibroelastosis	1
Anomalous left coronary artery	1
Coarctation of the aorta	1
Total	13

For example in small cyanotic infants the only logical operations are either (1) to increase pulmonary blood flow or (2) to increase mixing at the atrial level. The exact intracardiac anatomy is rarely of interest at this time.

3. Infants are catheterized with a clear plan of action. The procedure is kept to the minimum compatible with obtaining the information needed to establish the course of future management.

REFERENCES

1. Giammona, S. T., Lurie, P. R., and Segar, W. E.: Hypertonicity following selective angiocardiography, Circulation 28:1096, 1963.
2. Venables, A. W., and Hiller, H. G.: Complications of cardiac investigation, Brit. Heart J. 25:334, 1963.
3. Elliott, L. P., Best, E. B., and Schiebler, G. L.: Aortic atresia. A case report and review, Am. Heart J. 62:821, 1961.
4. Winchell, P.: Infectious endocarditis as a result of contamination during cardiac catheterization, New England J. Med. 248:245, 1953.
5. Lurie, P. R., and Grajo, M. Z.: Accidental cardiac puncture during right heart catheterization, Pediatrics 29:283, 1962.
6. Miller, R.: Personal communication.
7. Weinberg, D. I., Artley, J. L., Whalen, R. E., and McIntosh, H. D.: Electric shock hazards in cardiac catheterization, Circulation Res. 11:1104, 1962.
8. Starmer, C. F., Whalen, R. E., and McIntosh, H. D.: Hazards of electric shock in cardiology, Am. J. Cardiol. 14:537, 1964.
9. Vlad, P., Hohn, A., and Lambert, E. C.: Retrograde arterial catheterization of the left heart. Experience with 500 infants and children, Circulation 29:787, 1964.
10. Benson, R. W., Schiebler, G. L., Krovetz, L. J., and Satterer, W. F.: An electro-optical mean-concentrating system for a pressurized flush bottle, J. Appl. Physiol. 20:569, 1965.
11. Keith, J. D., and Moes, C. A. F.: Selective angiocardiography, in Zimmerman, H. A., editor: Intravascular catheterization, ed. 2, Springfield, 1966, Charles C Thomas, Publisher, Chap. 3, p. 225.
12. Zimmerman, H. A.: The technique of right cardiac catheterization, in Zimmerman, H. A., editor: Intravascular catheterization, ed. 2, Springfield, 1966, Charles C Thomas, Publisher, chap. 1, p. 3.
13. Lambert, E. C., Canent, R. V., and Hohn, A. R.: Congenital cardiac anomalies in the newborn. A review of conditions causing death or severe distress in the first month of life, Pediatrics 37:343, 1966.
14. Lambert, E. C.: Personal communication.
15. Read, R. C.: Cause of death in cardioangiography, J. Thoracic & Cardiovas. Surg. 38:685, 1959.

Qualitative effects of thoracic resistivity variations on the interpretation of electrocardiograms: The low resistance surface layer

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Although the torso is often assumed in electrocardiographic studies to be homogeneous, it is not. In a previous paper[1] we have considered the resistivity changes which produce the most drastic modification of surface electrocardiograms (ECG's). These are those variations which occur in and around the heart itself, i.e., the differences in conductivity between heart muscle, blood, and lung, as well as the lower resistivity of heart muscle in the direction of its fibers compared to that in a transverse direction.

In this article we discuss what we consider to be the second most important resistivity change, namely, that occurring in the vicinity of the surface electrodes. This is due to the relatively low resistance surface layer formed by the muscles girdling the thorax. As in our first paper, we use elementary models, and neglect the perturbing effects of other resistivity changes, e.g., the ribs, spine, sternum, liver, blood, blood vessels, pleural membranes, etc.

Experimental

Observed electrical characteristics of the surface layer. Fig. 1 shows a schematic representation of this low resistance layer. The skin and surface fat overlie the muscle which, in turn, overlies the lung. This muscle layer shows variations in thickness from approximately 1 to 3 cm. in anatomic cross section drawings.[2] In the region of the chest surface of greatest interest to us, over the heart, the "pectoralis major" muscles tend to run from the left shoulder-arm region toward the caudal rib cage and sternum. Of the muscles between the ribs, the "intercostalis externus" are oriented more or less vertically, and the "intercostalis internus" horizontally. Other nearby muscles, "pectoralis minor" and "serratus anterior," have still different orientations. Thus, the successive layers of muscle are by no means well aligned.

Electrical effects of this low-resistance layer are seen in measurements[3,4] of the over-all resistivity of the trunk made with currents flowing from head and shoulders to feet. Measurements of normal male adults have yielded values of 463 and 489 ohm-cm., which differ approximately by a factor of four from the value of 2,000 ohm-cm. found for dog lung. Comparisons of measurements of this type made on a

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dog[1] first with the chest intact and second with the chest opened and the lungs insulated by wrapping them with a plastic film have yielded a mean value for the resistivity of the surface layer of 281 ohm-cm.

The relative amplitudes of ECG's registered from human subjects also show effects similar to those which would be produced by a low-resistance layer. The average potential differences between a grid of electrodes covering the chest and another the back, were compared with the voltage in the chest back lead in the axial system for six subjects. It was found in all cases that the ratio of the peak amplitude of the axial lead to that of the grid lead was smaller than the sensitivity ratio determined with a homogeneous tank torso the same leads, and a dipole located at a position corresponding to the anatomical center of the heart. This sort of result would be expected were the "effective thickness of the surface layer many times its actual thickness.

Theoretical characteristics of the surface layer. The effects on the ECG of a layer of muscle can to some degree be predicted theoretically. So far as chest electrodes are concerned it is convenient here to make the simplifying assumption that the chest surface is flat rather than curved and infinite in extent. At first glance, this model may appear to be overly simplified. However one can easily extend results obtained with it to a box-shaped conductor through the use of multiple reflections of images in the box sides. Furthermore, experiments with rectangular tanks with and without rounded edges have shown that in most leads the effect of rounding is to change relative sensitivities by only a few per cent. In addition a quantitative estimate of the effect of curvature is possible in the case of a spherical surface layer. In the section entitled Effect of curvature of the surface layer it is found that the predictions obtained with the flat surface layer theory agree reasonably well with those obtained from the exact analysis of the sphere.

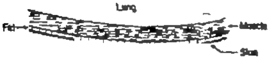

Fig. 1. Schematic cross section of torso surface layer.

A recently published survey by Geddes and Baker[2] of the resistivity of various tissues includes a number of measurements of muscle conductivity which show that the low frequency resistivity of muscle along the fibers is much less than across the fibers.

Measurements by Burger and van Milaan, Burger and van Dongen,[3] and by Rush and associates[4] have indicated that the former is about 150 ohm-cm and the latter 2,300 ohm-cm. So far as currents flowing parallel to the surface of the chest are concerned, this disparity between the high and low resistivity is greatly reduced

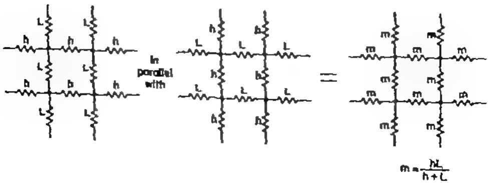

Fig. 2. Resistor matrices showing how two perpendicular anisotropic sheets yield an isotropic sheet when placed in parallel.

by the fact that successive laminas of muscle are oriented in different directions. In fact, if we use the simplifying assumption that the laminas are thin and of uniform thickness and run alternately at right angles to one another, we find that the resistivity parallel to the surface (in the limit as the thickness of the laminas approaches zero) no longer depends on the direction.[1] This is easily visualized from Fig. 2, where two two-dimensional resistor matrices, representing two adjacent anisotropic conducting sheets, are connected in parallel, the result being an isotropic resistance matrix. This shows that the conductivity σ_m of the melded layers is given by the means of the high (σ_h) and low (σ_l) conductivity, i.e., by $\sigma_m = \frac{1}{2}(\sigma_h+\sigma_l)$. This may be expressed in terms of corresponding resistivities, ρ, as $\rho_m = 2\rho_l\rho_h/(\rho_l+\rho_h)$. Taking the high and low resistivities of muscle to be 150 and 2,300 ohm-cm, respectively, we obtain an average isotropic resistivity ρ_m tangential to the surface of 280 ohm-cm. (the very close correspondence between this and the experimental value 281 ohm-cm, although fortunate, does not mean that our model is accurate within one half of 1 per cent!)

The conclusion that the muscle may be considered homogeneous in directions parallel to the surface is supported by the regular nature of constant potential lines on the body surface arising from passing current from head to foot. No indications of the underlying anisotropy are seen.[8] The component of current normal to the surface encounters a common high resistivity from all the muscles. With the mean value ρ_m representing the tangential resistivity and the high value ρ_h representing the resistivity normal to the surface of the body, a section of the muscle perpendicular to the surface can be represented by the resistance matrix shown in Fig. 3,*A*. Now, so far as the distribution in the network of currents introduced into it from outside is concerned, it would make no difference were this matrix stretched by a factor of $\sqrt{h/m}$ as is shown in Fig. 3,*B*. This stretching has the effect of making the voltage drop per centimeter in the h resistors for a given surface current density smaller. It thus decreases the effective resistivity of the medium represented by the network in the direction of the h resistors. The stretching increases the resistivity in the direction of the m resistors by the same factor. Since $\rho_m\sqrt{\rho_h/\rho_m} = \rho_h\sqrt{\rho_m/\rho_h} = \sqrt{\rho_m\rho_h}$, the stretching has the effect of making the two resistivities the same.

Furthermore, if the matrix in Fig. 3,*B* is sufficiently fine grained, it will make no *difference to external measurements if the* number of resistors in the direction perpendicular to the surface is increased provided that the resistivity of each resistor is reduced in proportion. Similarly, the number of resistors in a direction parallel

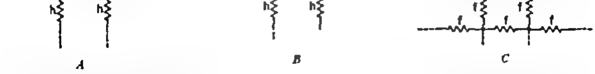

Fig. 3. Resistor matrices showing how the anisotropic surface layer represented by equivalent thicker isotropic layer. Each matrix represents a thin slice of the conductor perpendicular to the plane of the surface. *A*, Actual matrix. *B*, stretched matrix (stretch factor is $\sqrt{h/m}$). *C*, Isotropic square-celled matrix equivalent to stretched matrix.

to the surface can be increased providing that the resistance of each is increased in proportion. The result of these manipulations is the isotropic square-celled matrix shown in Fig. 3 C. This matrix represents a homogeneous isotropic surface layer of resistivity $\sqrt{\rho_m \rho_L}$ and of a thickness $\sqrt{\rho_L/\rho_m}$ times its original thickness. The result above was derived on a field theoretic basis for an infinite anisotropic slab by Kunz and Moran.[11]

According to this analysis a muscle layer 1 cm. thick having a resistivity perpendicular to its surface of 2,300 ohm-cm. and 280 ohm-cm. parallel to its surface will act as if it were a layer $\sqrt{2{,}300/280} = 2.85 \cong 3$ cm. thick having a resistivity of $\sqrt{2{,}300 \cdot 280} = 800$ ohm-cm. Of course, if the muscle fibers do not run precisely parallel to the surface, ρ_L will be lower and there will be less increase in the effective thickness.

Effect of low-resistance surface layer on the lead field of an exploring electrode. Perhaps the simplest situation to which these results can be applied is that shown in Fig. 4. Here the lead consists of an exploring electrode on the chest surface coupled with an ideal indifferent electrode presumed to be located at infinity.

If the surface layer is anisotropic, we have already seen how its apparent thickness will be increased and its effective resistivity changed. Our analysis gave a value of 800 ohm-cm. and a thickness of 3 cm. for this layer of augmented thickness. As 800 ohm-cm. is substantially smaller than lung resistivity, we determine here the effect of this residual difference.

The analysis in Appendix I shows that the field produced in the lung by the surface electrode may be considered to be produced by a number of sources in an infinite homogeneous conductor. These are of progressively diminishing size and increased remoteness located on a line passing through the exploring electrode perpendicular to the surface (Fig. 11,*B*). At points in the lung relatively remote from the electrode these sources may be grouped together into a single equivalent source whose source strength is the same as that of the actual exploring electrode and which is located at a distance from the bottom surface of the surface layer (Fig. 4) increased over the actual distance by a factor given by the ratio (ρ_l / ρ_{eff}) of the resistivity of the lung to that of the effective surface layer.

These statements regarding the lead field of the exploring electrode have a simple interpretation in electrocardiography. First, a low resistance surface layer tends to make the voltages measured on the surface smaller than they would be in a homogeneous conductor because of an increase in effective distance to the EMF's in the heart. The increased distance also acts to reduce proximity effects and to reduce the surface manifestations of multiplicity in the sources which in reality comprise the heart's electrical generator.

A more accurate approximation for the field of an exploring electrode on a low-resistance surface layer. In regions of the lung close to the exploring electrode the approximations used for points remote from the exploring electrode can be improved upon substantially. For example, in Appendix II we compute the field in the lung (2,000 ohm-cm.) at a point P located 5 cm. below the undersurface of a 1 cm. thick anisotropic muscle layer whose effective isotropic thickness is 3 cm. and resistivity 800 ohm-cm. The calculated lead field density at this point as well as others at 3, 4, 6, and 7 cm. from the low resistance layer are plotted as heavy dots in Fig. 5. By way of contrast, curve *A* shows the field which would exist in this region were the surface layer

Fig. 4. Simple model for determining the lead field of an exploring electrode.

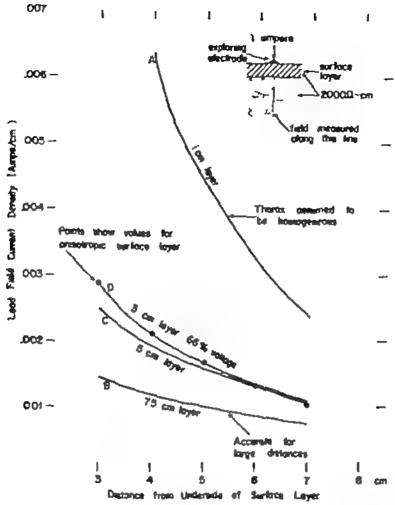

Fig. 5. Figure representing the main conclusions of this article. It shows how an anisotropic low-resistance surface layer (muscle) can be represented by a thicker surface layer having the same resistivity as the underlying medium (lung). The dots show the field calculated for an anisotropic 1 cm. surface layer. Curve A is the field which would exist with the 1 cm. surface layer of 2,000 ohm-cm. resistivity. This curve shows that lead sensitivity estimated with homogeneous models may be three times greater than actual sensitivities. Curves B and C are similar to A except for layer thickness. Curve C is the basis of the simple, reasonably accurate rule of thumb that a 1 cm. thick muscle layer over the heart is equivalent to 5 cm. of lung. Curve D represents the best approximation to the actual values (dots) and is described in text.

1 cm. thick and of the same resistivity as the underlying medium. We note that the actual field 5 cm. below the underside of the surface layer, a position roughly corresponding to the center of the heart, is only 38 per cent of the field that would exist there were the entire conductor homogeneous. Obviously, the assumption that the thorax acts as if it were homogeneous leads to gross errors.

Curve *B* shows the field which would be produced if the thickness of the equivalent isotropic 3 cm. surface layer were increased by a factor of 2½ to 7½ cm. and its resistivity made the same as the rest of the conductor. This curve gives a better estimate of the actual field than curve *A*, but is by no means precise.

In curve *C* the surface layer thickness is taken to be 5 cm. rather than 7½ cm. The approximation here is quite respectable.

Curve *D* is that obtained with a 3 cm. surface layer whose resistivity has been changed to match the rest of the medium and whose lead field source strength has been reduced to two thirds of an ampere. This curve gives an excellent approxima-

tion of the actual field directly under the electrode. (It can be shown theoretically that if the field is a good match to the actual field on this axis, it will be a good match off the axis also.) The reduced lead field strength implies that the voltages that will be measured in the region of the heart with an exploring electrode directly over the heart will be almost identical to two thirds of the voltages which would be measured were that surface layer replaced with a 3 cm. surface layer having the same resistivity as the underlying medium.

We have assumed that a high degree of anisotropy exists in the surface layer. As a limiting contrary case we might suppose that the anisotropy is negligible and that the resistivity in all directions is 280 ohm-cm. This is the value estimated from experimental data for current flow in a tangential direction. The field is computed as outlined in Appendix II. It is found in a manner similar to that of curve *D* of Fig. 5 that the actual field can be very well approximated by assuming that the surface layer thickness has been increased from 1 to 2.5 cm., giving it the same resistivity as the rest of the medium and by decreasing the lead field source strength of the electrode from 1 to 0.7 amperes. These values do not differ much from the 3 cm. and 0.67 amperes shown in curve *D* which were determined for the anisotropic layer.

Effect of curvature of the surface layer. Do these conclusions, derived from flat surface layers, also apply to curved layers? To gain insight into this question, we derive, in Appendix III, an equation for the lead field at the center of a homogeneous sphere enclosed in a spherical shell of lower resistivity into which current flows via electrodes located on opposite sides of the sphere. (This is the inverse of a problem solved by Bayley and Berry.[13]) The sphere and its surface layer form a crude model of the body whose dimensions have been chosen to match the flat surface layer case already considered. We assume that the inner sphere has a radius of 5 cm. and resistivity of 2,000 ohm-cm. The shell is taken to be anisotropic, 1 cm. thick, and also is assumed to be representable with good approximation by a layer 3 cm. thick of 800 ohm-cm. isotropic resistivity.

We find from Equation (26) in Appendix III that the introduction of a unit current will produce a field of 0.00435 amperes per square centimeter at the sphere's middle. On the other hand, were the sphere and shell of the same resistivity, and of total radius 8 cm., the central field strength would be 0.0135. The actual value 0.00435 is 32 per cent of this. Thus, we find in the sphere roughly the same degree of reduction (38 per cent) found with a flat surface layer. The reduction is somewhat greater for the sphere in part because some of the lead field current which otherwise would pass through the center has been drawn away to the low resistance sides of the sphere.

In any case, the values are enough alike to indicate that what is true for a flat layer is also true for a curved layer.

Exact compensation for the low-resistance surface layer in ideal leads. Through the use of electrodes covering the entire surface of a homogeneous volume conductor connected together via appropriate resistor networks, it has been shown[8,9] that it is possible to construct leads whose lead fields are ideal. For example they may be (1) uniform, corresponding to heart vector leads, or (2) appear to radiate out from a point, corresponding to unipolar leads, or (3) have a point of zero field corresponding to "null cancellation" or quadripole leads. Furthermore, it has also been shown[14] that these and other types of lead fields may be produced in a region corresponding to the heart even if the latter has a resistivity different from that of the rest of the body and is spherical or ellipsoidal in shape. Finally, leads may, in principle, be constructed under these assumed conditions in which the exploring electrode appears to be within the volume conductor close to the heart, despite the fact that all electrodes are on the body surface.

These objectives may still be achieved when there is an effectively homogeneous low-resistance surface layer whose inner surface is ellipsoidal in shape. We will present here examples which should, along with the references cited, serve to convey the idea behind the mathematical approach which is based on the lead field concept.

Consider a sphere bounded by a low resistance surface layer in the form of a *spherical shell of uniform thickness.* Suppose there exists in the sphere proper a uniform lead field. Then, as was discussed in the appendix of the previous article[1] the lead field in the outer spherical shell will be that of a dipole plus a uniform lead field. (The sources are outside the shell.) If one constructs a lead to introduce or remove the part of this lead field current which arrives or leaves at the outer surface of the spherical shell, then the uniqueness theorem requires that this external lead produce the desired uniform field within the sphere.

The same argument may be applied to lead fields of various types in the inner sphere, as for example the unipolar lead type, the null lead type, etc. These may be broken down into spherical harmonic components (uniform, dipolelike, etc.) each of which propagates into the spherical shell a fixed combination of components which when summed will yield a surface field on the outer surface of the spherical shell which can be matched by a properly designed lead. That lead will therefore produce the desired field in the sphere.

It is a small generalization of this procedure, conceptually speaking, to drop the assumption that the outer shell is uniform in thickness with a spherical outer surface. Even if the outer surface is irregular, the identical procedure may be followed to construct a lead which introduces the required lead field surface current. Furthermore, this type of approach can be extended to ellipsoidal shapes by using ellipsoidal harmonics, rather than spherical harmonics. Fig. 6 illustrates this possibility. The procedure is the same when all surfaces are ellipsoids or spheres (except the outer surface which may have any shape whatever) and the conductivity in each region is homogeneous and isotropic.

Approximate compensation for the low-resistance surface layer. As a practical matter, what needs to be done to adapt ideal leads to the presence of a low resistance surface layer is to provide extra lead field current for the portions of the layer *that run parallel* to the direction of the lead field. This extra current is needed

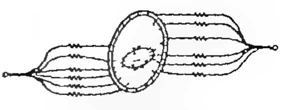

Fig. 6. Cross section of heterogeneous conductor showing how a uniform lead field can nevertheless be produced inside an ellipsoidal homogeneous heart.

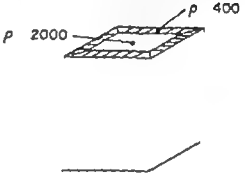

Fig. 7. Model illustrating the shunting effect of low resistance layer on the neck-foot lead.

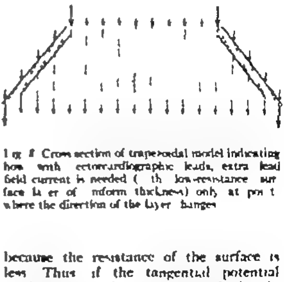

Fig. 8. Cross section of trapezoidal model indicating how, with vectorcardiographic leads, extra lead field current is needed (with low-resistance surface layer of uniform thickness) only at points where the direction of the layer changes.

because the resistance of the surface is less. Thus, if the tangential potential gradient in the layer is to match that in the body proper, additional current must be supplied.

As an example, consider the box-shaped conductor shown in Fig. 7, which is covered with a low resistance surface layer of uniform thickness. A lead for inducing a uniform vertical field in the box must provide five times as much current density for the sides of the box as for the center. Hence, a

properly designed lead would employ resistors for electrodes feeding the surface layer parallel to the lead field having five times the conductance of those feeding other parts of the conductor

In a conductor having a trapezoidal cross section as shown in Fig 8 in a case where one wishes to produce a uniform lead field in the body proper the lead field current in the layer may be divided into two components (1) a component of current flowing perpendicularly across the layer which supplies the normal component of the lead field flowing into the body proper and (2) a component of current flowing along the layer parallel to its surface This component maintains the same tangential potential gradient in the surface layer as is required by the uniform lead field in the body proper

When the field desired in the body proper is nonuniform the same approach may be employed provided that the surface layer is thin enough so that the normal component of the field on its outer surface may be considered the same as that on its inner surface

It is clear that, when the internal field is uniform component 2 of lead field current, i.e., the total current flowing tangential to the low-resistance surface layer needs to be augmented or diminished by extra current from the surface electrodes only in regions where the surface layer changes direction i.e., curves. In general a curved layer may be represented as a series of straight sections. The extra surface current required may be introduced at the points where the various segments meet.

Discussion

The effect of the low resistance surface layer may be summarized qualitatively in the following manner In the neighborhood of the electrodes, the layer tends to spread the lead field current out over a larger area, thus making the electrode seem to be further away and the field within the body weaker Along the sides of the body the low resistance layer tends to shunt the lead field from the central portion of the body once again making the internal lead field seem weaker Both of these effects can be predicted if one views the low-resistance layer as an effectively thicker layer having the same resistivity as the underlying tissue

The weakening of the lead field in the neighborhood of the heart is quite substantial. We have already considered several cases in which the field is reduced to about one third the value it would have were the surface layer resistivity the same as that of the underlying medium. Consider further a head foot lead (Fig 7) If one assumes that the resistivity of the lungs is 2 000 ohm-cm. that the tangential resistivity of the surface layer is 280 ohm-cm and that the cross sectional areas of the two with regard to head foot lead field currents are 400 and 180 cm.^{2} respectively then the current which flows in the lung will be $(400/2{,}000)/[(400/2\,000)+(180/280)]$ of the total i.e. 23 7 per cent rather than the 66 per cent it would be were the trunk homogeneous. Thus, the low resistance surface layer here also diminishes the sensitivity of this lead by a factor of about three, as compared to what would exist were the body homogeneous.

It is not our intention to arrive at quantitative conclusions using the simple models considered in this paper but they do indicate that the effect of the low resistance layer is to reduce the internal lead fields to values substantially less than one half of those found with homogeneous models. Furthermore the reduction factors are not necessarily the same in the different leads. Clearly this is a consideration that should not be ignored in electrocardiographic interpretation or in lead system design.

Conclusion

The surface of the body is covered by a layer of muscle whose thickness varies greatly from point to point as well as from subject to subject. Because the resistivity of the muscle in the direction of the fibers is low about the same as blood and across the fibers high, the same as lung and because it differs in any case from that of lung this layer has a marked effect on the interpretation of ECGs.

Studies with simple theoretical models in this paper indicate that this layer may be considered as a rough approximation to have the same resistivity as the under

lying tissue (lung) provided that it is also considered to have a thickness of the order of three to seven times its actual thickness (see Fig 5) A muscle layer 1 cm thick as might be typical for the region over the heart appears to be about 5 cm thick.

As a result of this increased effective distance between the heart and the surface electrodes the sensitivity of the lead is reduced to a value generally less than one half the value which would exist were there no difference in resistivity between the surface layer and lung Furthermore proximity effects are substantially reduced also. As the sensitivity reduction factor depends upon the lead considered this means that heterogeneous models must be employed for accurate determination of sensitivity factors of vectorcardiographic leads

An opposite effect is produced by the low resistance of blood and heart muscle relative to lung which tends to increase the sensitivity (on the average) Fig. 1

REFERENCES

1 McFee R and Rush, S Qualitative effects of thoracic resistivity variations on the interpretation of electrocardiograms The Brody effect, Am Heart J 74:642 1967
2 F leshymer H C and Schoemaker D M A cross-section anatomy New York 1911 Appleton-Century-Crofts.
3. Schmitt O H Lead vectors and transfer impedance A New York Acad. Sc. 65 1109 1957
4 [illegible] h, S., Abildskov J A and McFee R Resistivity of body tissues at low frequencies, Circulation Res. 12:40, 1963
5 McFee R and Parungao, A. A orthogonal lead system for clinical electrocardiography Am. Heart J 62:93 1961
6. Bayley R. H Electrocardiographic analysis, Vol 1 Biophysical principles of electrocardiography New York, 1958, Paul B Hoeber Inc. p. 211
7 Geddes L. A., and Baker L. E. The specific resistance of biological material. A compendium of data for the biomedical engineer and physiologist, Med. & Biol. Eng 5:271 1967
8. Burger H C., and van Milaan, J B Measurement of the specific resistance of the human body to direct current Acta med. scandinav 114:584 1943
9 Burger H C., and van Dongen, R Specific electrical resistance of body tissues, Phys Med. & Biol. 5:431 1961
10. Rush, S.: A principle for solving a class of anisotropic current flow problems and applications to electrocardiography IEEE Tr Biomed. Eng 11 18, 1967
11 Kunz, K. S., and Moran, J H : Some effects of formation anisotropy on resistivity measurements in boreholes, Geophysics 23 770, 1958.
12 Bayley R. H and Berry P M : Changes produced in the resultant "heart vector by the non-homogeneous volume conductor with normal specific resistivities, Proc. of the Long Island Jewish Hosp. Symposium on vectorcardiography Amsterdam 1965 North Holland Publishing Co. p 109
13 McFee, R. and Johnston, J D Electrocardiographic leads III Circulation 9:868, 1954
14 McFee, R.: Analysis and synthesis of electrocardiographic leads, Ph.D Dissertation (Electrical Engineering) University of Michigan Ann Arbor 1954
15 Slater J C., and Frank, N H Electromagnetism, ed 1 New York, 1947 McGraw Hill Book Co. Inc. p. 47
16. Smythe, W R Static and dynamic electricity ed. 2 New York, 1950 McGraw Hill Book Co., Inc., p. 239

Appendix I

General equations for the lead field of an exploring electrode (unit point current source) on a flat low-resistance surface layer If there is a unit source in a semi infinite homogeneous conducting medium bounded by a conducting or insulating plane (Fig 9 *A*) then the effect of the plane can be taken into account by pretending that the medium is infinite in all directions and that there is an image source located as shown in Fig 9 *B*

Note that if the source is on the surface it and its image merge and the effective strength of the source is doubled

If the infinite medium is separated into two halves, one with resistivity α and the other β (Fig 10 *A*) with a source in the α region then the field in the α region will be that of the original source plus an image of strength $c = (\beta-\alpha)/(\alpha+\beta)$ times the original source as shown in Fig 10 *B* In the β region the strength of the original source will appear to be reduced by a factor $k = (1-c)$ Here c is the reflection factor and k is the transmission factor An electrostatic analogue of this problem is treated by Slater and Frank.[15]

Straightforward use of these results shows that in the case of Fig 11 *A* the field in the β region will appear to originate from an infinite number of sources representing the original source of doubled strength attenuated by a factor k its

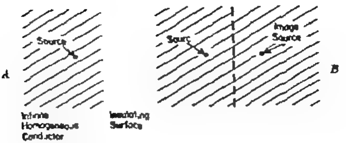

Fig. 9 An insulating surface produces an image.

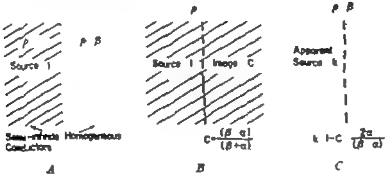

Fig. 10 A change in resistivity produces an "image." A Actual situation. B equivalent situation as viewed from region. C equivalent situation as viewed from β region.

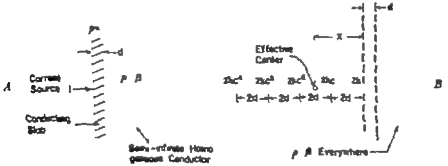

Fig. 11 Image sources for unit source of current connected to the outside surface of low-resistance surface layer. A Actual situation; B equivalent situation as viewed from β region.

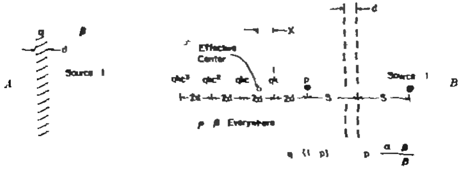

Fig. 12 Image sources for unit source of current located inside conductor near low-resistance surface layer. A Actual situation. B equivalent situation as viewed from β region.

$$g = 2k + 2kc + 2kc \ + 2kc \ + \qquad = 2k/1\text{-}c = 2k/k = 2 \tag{1}$$

$$\begin{aligned} \Sigma\, i\, \vec{r} &= 2k(x) + 2kc(x - 2d) + 2kc \ (x - 4d) + \\ &= 2k(1 + c + c \ + \qquad)\, x - 4dkc(1 + 2c + 3c \ + \qquad) \\ &= (2k \ 1 - c)\, x - [4dkc/(1 - c)^2] \end{aligned} \tag{2}$$

attenuated doubly reflected image 2kc, the re-reflected image $2kc^2$ etc the entire conglomeration being located in an apparent infinite homogeneous medium of resistivity β

This apparent infinite series of sources will itself appear as a single apparent source if the point of measurement is sufficiently far away The strength g of this approximate apparent source will be equal to the sum of the strength of all its components as in Equation (1) We will define its effective position x to the left of the first source k as that position about which the dipole moment $\Sigma i_n \vec{r}$ of the series of sources is zero Here i is the strength of the nth source in amperes and $\vec{r}$ its position vector relative to an arbitrary coordinate system (If a unit source were placed at this position its remote lead field would then match the actual field with minimum error) Thus we find as in Equation (2)

If we set this to zero we obtain

$$0 = x - (2dc/k) \tag{3}$$

This gives for x

$$x = d(\alpha\text{-}\beta)/\beta \tag{4}$$

Thus the effective center of the infinite series of charges is at distance

$$x + d = d(\alpha/\beta) \tag{5}$$

to the right of the boundary between the surface slab and the underlying medium This means the effective slab thickness has been increased by (α/β)

In the same way one can treat the case analogous to esophageal leads where the current source is in the underlying medium as shown in Fig 12 *A* Here the roles of the resistivities of the two media are reversed and to avoid confusion we have replaced the c and k factors defined in Fig 10 by p and q factors, respectively Analysis of the reflections and re-reflections involved in this situation leads to the infinite series of sources shown in Fig 12 *B* The first image generated at the α-β boundary is of strength p. The second due to the transmitted effect q of the internal unit source is totally reflected at the outer boundary and transmitted back to the internal medium with additional attenuation k yielding effective source strength qk. This second image is also responsible for the third and higher order images (qk)c $(qk)c^2$ etc

The electrical center of this group of sources can be determined once again by choosing x its distance measured to the left of the qk source so that the dipole moment $\Sigma(i\,\vec{r}\,)$ of the cluster is zero This requires that

$$0 = M = p(x + 2d) + qkx + [qkc(x - ad) + qkc \ (x - 4d) + qkc^3 (x - 6d) + \qquad] \tag{6}$$

This may be rewritten as

$$0 = px + 2pd + qk(1 + c + c^2 + \qquad)\, x - 2qkdc(1 + 2c + 3c \ + 4c \ + \qquad) \tag{7}$$

which in turn may be simplified to yield

$$0 = px + 2dp + qk/(1 - c)\, x - 2qkdc/(1 - \ c) = -2d\left(\frac{\beta}{\alpha} - 1\right) + x \tag{8}$$

The distance between this effective electrical center and the internal source which we will designate as 2s will be twice the distance s from the source to the effective reflecting surface which would

exist were the medium homogeneous with resistivity β. This distance is

$$2s = x + 2d + 2s = 2d\left(\frac{\beta}{\alpha}\right) + 2s \qquad (9)$$

Thus the field in the underlying medium acts as if there were a reflecting (insulating) surface at a distance

$$s = s + d\left(\frac{\beta}{\alpha}\right) \qquad (10)$$

It is clear from this equation that the lower resistivity of the surface layer makes it appear as if the surface is thicker by a factor of $(\frac{\beta}{\alpha})$, the entire conducting medium being considered homogeneous with the same resistivity as the underlying medium.

Appendix II

Sample calculation of the lead field under an exploring electrode on a flat isotropic low-resistance surface layer. We assume first that the layer is 3 cm. thick, has a resistivity of 800 ohm-cm., and covers a semi-infinite medium of resistivity 2,000 ohm-cm. We are interested in the field at points P_3, P_4, P_5, P and P which are located 3, 4, 5, 6, and 7 cm. respectively from the bottom surface of the low-resistance layer directly under the exploring electrode.

As a sample calculation, let us consider the field at P_5. As shown in Appendix I we may consider this point to be part of an infinite homogeneous conductor of 2,000 ohm-cm., provided that we consider the sources of the field to be those shown in Fig. 11, B. Determining k and c with the equations shown in Fig. 10, we find for them values of (4/7) and (3/7) respectively. The nearest source is located (5+3) cm. from P and according to Fig. 11, B has strength 2k or 2(4/7) amperes. The next most distant source is located (5+3+6) or 14 cm. from P_5 and has strength 2kc or 2(4/7)(3/7) amperes. The field density at P can be determined using the equation for the field of a source in an infinite homogeneous conductor

$$J = I/4\pi r \qquad (11)$$

where J is the current density (amps per square centimeter), I the source strength (amperes), and r the distance (centimeters). In our case we must sum the effects of many sources and thus obtain for a unit source

$$J =$$

$$[2(4/7)/4\pi(8)] + [2(4/7)(3/7)/4\pi(14)] +$$

$$[2(4/7)(3/7)/4\pi(20)] + \qquad (12)$$

The value of this is found to be 0.00167 amps per square centimeter and is plotted in Fig. 5 along with the values for the other points P through P.

Appendix III

Field of point current sources on the surface of concentric spheres. In this appendix we determine the lead field at the center of a conducting sphere of radius a (simulating the rib cage and interior) which is surrounded by a concentric conducting shell of outer radius b (simulating the skeletal muscle, fat, and skin) which in turn is imbedded in an insulating medium (air). The field arises from a current source and sink lying at the surface of the shell at opposite ends of a diameter. The resistivity of the inner sphere is σ and of the outer shell σ_2. Both are assumed isotropic.

The derivation is an extension of that given in Smythe[14] for a single sphere. The potential Φ_1 inside the solid sphere, medium (1), satisfies Laplace's Equation and in spherical coordinates is

$$\Phi = \sum_{n}^{\infty} C_n r^n P_n(\cos\theta) \qquad (13)$$

r is the spherical coordinate radius and $P_n(\cos\theta)$ the Legendre Polynomial. The electrodes are located on the line $\theta = 0$. In the shell a slightly more general solution of Laplace's Equation is required and can be expressed

$$\Phi = \sum_{n}^{\infty}\left(A_n r^n + \frac{B_n}{r^{n+1}}\right) P_n(\cos\theta) \qquad (14)$$

At the boundary r = a, the potentials and normal current densities are continuous. Thus,

$$\Phi_1(a) = \Phi_2(a) \qquad (15)$$

and

$$\sigma_1 \frac{\partial \Phi_1}{\partial r} = \sigma_2 \frac{\partial \Phi_2}{\partial r} \tag{16}$$

in which σ_1 and σ_2 are conductivities in media (1) and (2).

The insertion of Equations (13) and (14) into the boundary conditions of Equations (15) and (16) leads to the coefficient relationships

$$A + \frac{B}{a^{2n}} = C_n \tag{17}$$

$$1 - \left(\frac{n+1}{n}\right)\frac{B}{a^{2n+}} = C_n\left(\frac{\sigma}{\sigma}\right) \tag{18}$$

The remaining boundary condition is found from the normal component of current at $r = b$. This is zero everywhere except at the electrodes. We note that because of the symmetry only odd Legendre Polynomials are required. Thus at the surface the normal current density from Equation (14) is

$$\sigma \frac{\partial \Phi_2}{\partial r} = \sigma \sum_{n}^{\infty} \left[(2n+1)\ 1_{2n+}\ b^{2n} - \frac{2(n+1)}{b^{2n}} B_{2n+} \right] P_{2n+} \ (\cos\theta) \tag{19}$$

To obtain a relation among the A's, B's and total current I, both sides of Equation (19) are multiplied by P_{2n+1} $(\cos\theta)$ and integrated with respect to cos θ from 0 to 1. This procedure gives us Equation (20).

$$\int \sigma \frac{\partial \Phi_2}{\partial r} P_{2n+} \ (\cos\theta)\, d(\cos\theta)$$

$$= \sigma \left[1_{2n} \quad (2n+1)\, b^{2n} - \frac{2(n+1)}{b^{2n}} B_{2n+} \right] + \int [P_{2n+} \ (\cos\theta)]^2\, d(\cos\theta) \tag{20}$$

The integral on the left hand side, in which $\frac{\partial \Phi_2}{\partial r}$ is zero except at the point electrode, can be recognized as $[I/2\pi b^2]$, while the integral on the right is available as $[4n+3]$.[1]
Thus, Equation (20) leads to

$$1_{2n} \quad (2n+1)\, b \quad - \left(\frac{2(n+1)}{4n+3}\right) \frac{B_{2n+}}{b^{\ +}} = \frac{I}{\sigma \pi b^2} \tag{21}$$

Equations (21), (18), and (17) can be used to find the coefficients as

$$B_{2n+} = C \qquad a^{4n+} \left(\frac{\sigma - \sigma}{2}\right)\left(\frac{2n+1}{4n+3}\right) \tag{22}$$

$$1_{\ +} = C_{2n} \quad \frac{2\sigma\,(n+1) + \sigma\,(2n+1)}{\sigma\,(4n+3)} \tag{23}$$

$$C_{2n+} = \frac{I\,(4n+3)}{2\pi\,(2n+1)}\, b^{\ +} \left[b \qquad [2\sigma\,(n+1) + \sigma\,(2n+1)] - (\sigma - \sigma)\,2\,(n+1)a^{4n+} \right]^{-} \tag{24}$$

Use of Equation (24) in Equation (13) gives

$$\Phi = \frac{I}{2\pi b\sigma} \sum_{n=0}^{\infty} \left(\frac{r}{b}\right)^{2n} \quad \left(\frac{4n+3}{2n+1}\right) \frac{P_{\ +}\ (\cos\theta)}{(1+D)} \tag{25}$$

in which

$$D = \left(\frac{2(n+1)}{4n+3}\right)\left(\frac{\sigma - \sigma}{\sigma}\right)\left[1 - \left(\frac{a}{b}\right)^{4n+}\right]$$

When the gradient of Equation (25) is taken converted to rectangular coordinates and multiplied by the conductivity σ_1, to obtain the current density J_o, at the origin that quantity is

$$J\,(O) = -\frac{I}{2\pi b^2}\left[\frac{3}{1 + \frac{2}{3}\left(\frac{\sigma - \sigma}{\sigma}\right)\left(1 - \left(\frac{a}{b}\right)^3\right)}\right] \tag{26}$$

From Equation (26) the current densities at the origin for a sphere and shell $\sigma_1 \pm \sigma$ and a sphere alone $\sigma = \sigma$ can be found.

Variability of electrocardiographic data recorded with orthogonal leads

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The major potential advantage of using accurate orthogonal leads for recording electrocardiograms is that such leads should minimize distortion and variation due to differences in location of the cardiac dipole source or to noncardiac factors.[1] This should make it easier to directly relate electrocardiographic data to electrical events within the heart and may result in improved discrimination between records from normal and diseased subjects. Several orthogonal lead systems have been proposed for clinical use and their effectiveness in minimizing distortion due to eccentric location of the cardiac dipole has been evaluated in experiments with torso models.[-4]

The orthogonal leads described by Frank[3] have been used in many recent clinical studies, although some evidence suggests that Schmitt SVEC III[4] and McFee and Parungao axial leads may be more effective in minimizing variation due to differences in position of the cardiac dipole or chest electrodes.[4,7] Preliminary observations in the present study indicated that SVEC III leads were probably not well suited for routine use because of the technical problem of accurately placing the large number of chest electrodes, while the axial leads were only slightly less convenient to use than Frank leads. It was therefore decided to compare intra- and inter-individual variation in records obtained with Frank and axial leads to determine whether significant differences between the two lead systems could be demonstrated.

Relationships between data recorded with Frank leads and some constitutional variables were also analyzed in a group of normal subjects.

Table I. Age distribution for 305 normal Caucasian men

Age	Number
20 t 29	[illegible]
30 to 39	50
40 to 49	103
50 to 59	60
60 t 73	37
Total	305

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Materials and methods

Technically satisfactory Frank and axial lead records were obtained from 25 hospitalized patients with the chest electrodes placed at the level of both the fourth and the sixth intercostal space and from 22 patients with the lateral chest electrodes placed both 3 cm anterior and 3 cm posterior to the correct location.

Frank, axial, and standard 12 lead electrocardiographic data were recorded from a group of normal male students who volunteered at the time of a college entrance health examination. Frank and standard lead records were also available from a group of clinically normal male participants in the Los Angeles Heart Study. Characteristics of the students and participants in the Los Angeles Heart Study have been described previously;[illegible] only normotensive Caucasian men were included in the present normal groups (Table I).

The normal subjects were considered to have light or heavy relative body weight if their ponderal index (height in inches divided by the cube root of weight in pounds) was more than ½ standard deviation from the mean, and were considered to have small or large anteroposterior chest diameter if this measurement was more than ½ standard deviation from the mean.

Frank and axial lead data were recorded on magnetic tape and analyzed with a modification of the computer program described by Pipberger and associates.[illegible] Some visual measurements were also made

Table II. Standard deviations of differences recorded with displacement of Frank lead and axial lead electrodes

	Chest electrodes moved from fourth to sixth intercostal space (25 cases)				Lateral lead electrodes moved antero-posterior 6 cm. (22 cases)			
	Frank		Axial		Frank		Axial	
	S.D.	S.D. × 100 / Mean	S.D.	S.D. × 100 / Mean	S.D.	S.D. × 100 / Mean	S.D.	S.D. × 100 / Mean
Scalar magnitude (mv.)								
Rx	0.22	22	0.18	12	0.20	24	0.41	29
Ry	0.07	13	0.07	12	0.05	8	0.07	10
Sx	0.31	35	0.32	25	0.16	18	0.10	7
Spatial magnitude (mv.)								
QRS 0.02 sec.	0.14	38	0.14	31	0.12	39	0.11	25
QRS 0.03 sec.	0.24	34	0.[illegible]	19	0.14	23	0.27	32
QRS 0.04 sec.	0.35	30	0.30	19	0.24	22	0.55	36
Maximal QRS	0.26	[illegible]	0.23	11	0.14	10	0.27	12
Maximal T	0.08	27	0.09	18	0.05	15	0.05	10
Azimuth (degrees)								
QRS 0.02 sec.	30		18		40		32	
QRS 0.03 sec.	21		15		30		59	
QRS 0.04 sec.	32		28		27		32	
Maximal QRS	25		34		40		35	
Maximal T	13		18		8		9	
Elevation (degrees)								
QRS 0.02 sec.	20		10		14		11	
QRS 0.03 sec.	14		6		7		9	
QRS 0.04 sec.	5		4		8		12	
Maximal QRS	9		7		12		12	
Maximal T	15		9		7		5	

Table III Comparison of Frank lead and axial lead records from 70 normal subjects 20 to 39 years of age

	Frank leads			Axial leads			Correlation	
	Mean	S.D.	S.D. × 100 / Mean	Mean	S.D.	S.D. × 100 / Mean	(1 & 2) r	Δ (1-2) p <
Scalar magnitude (mv.)								
Rx	1.08	0.34	32	1.56	0.40	26	0.90	0.001
Ry	1.00	0.37	37	1.24	0.50	40	0.98	0.001
Sz	0.90	0.30	33	1.10	0.42	38	0.55	0.001
Spatial magnitude (mv.)								
QRS 0.02 sec.	0.36	0.15	42	0.42	0.15	36	0.73	0.001
QRS 0.03 sec.	0.66	0.23	35	0.87	0.28	32	0.77	0.001
QRS 0.04 sec.	1.36	0.35	26	1.74	0.46	26	0.64	0.001
QRS 0.05 sec.	1.40	0.46	33	1.81	0.61	34	0.84	0.001
Maximal QRS	1.65	0.40	24	2.17	0.49	23	0.82	0.001
SÂQRS (sec.)	37.1	11.8	32	50.2	16.3	32	0.73	0.001
Maximal T	0.54	0.16	30	0.74	0.24	32	0.78	0.001
SÂT (uvsec.)	62.3	19.5	31	87.7	27.8	32	0.84	0.001
Azimuth (degrees)								
QRS 0.02 sec.	84	22		93	21		0.86	0.001
QRS 0.03 sec.	29	26		42	25		0.79	0.001
QRS 0.04 sec.	344	23		4	25		0.50	0.001
QRS 0.05 sec.	311	27		331	35		0.71	0.001
Maximal QRS	327	25		349	34		0.56	0.001
SÂQRS	314	24		337	34		0.62	0.001
Maximal T	38	15		39	14		0.71	
SÂT	44	15		43	13		0.71	
Elevation (degrees)								
QRS 0.02 sec.	−3	16		−1	18		0.82	
QRS 0.03 sec.	19	14		15	13		0.88	0.001
QRS 0.04 sec.	35	11		31	12		0.71	0.001
QRS 0.05 sec.	35	14		33	15		0.81	0.05
Maximal QRS	*37*	*13*		*33*	*13*		*0.89*	*0.001*
SÂQRS	30	24		33	20		0.81	
Maximal T	27	8		25	9		0.84	0.001
SÂT	23	10		23	10		0.73	

from direct writer tracings of both orthogonal and standard lead data. Methods and equipment used to analyze the data have been described previously.[9] Comparisons between lead systems were based on records obtained in immediate succession to each other. Differences between means were evaluated by the use of t tests.

Linear statistical analysis of angular measurements can result in serious errors if the distribution encompasses most of the 360 degree range or the region of 0 degrees.[11] Two cases with an extreme value for an azimuth measurement were excluded from the present series of normal subjects to avoid this problem and the frame of reference for computation of azimuth statistics was shifted 180 degrees for the same reason.

Results

Movement of the chest electrodes from the level of the fourth intercostal space to the sixth intercostal space resulted in changes in scalar and vector magnitudes that had larger coefficients of variation.

*Coefficient of variation = standard deviation × 100/mean.

Table IV. Coefficients of variation for measurements of standard, Frank and axial lead records from 70 normal subjects 20 to 39 years of age

	Coefficients of variation $\frac{S.D \times 100}{Mean}$
Magnitude (mv.)	
Standard leads	
R	29
S_V	27
R + S_V	26
T_{V3}	29
Frank leads	
Rx	34
Sz	34
Rx + Sz	23
T	46
Axial leads	
Rx	27
Sz	38
Rx + Sz	20
T	39

with Frank than with axial leads (Table II). The changes with each lead system were very large in a few subjects. Movement of the electrodes from the level of the fourth to the sixth intercostal space was associated with a clockwise shift of 13 to 19 degrees in mean azimuths for QRS vectors recorded with Frank leads and no significant change with axial leads.

Movement of the lateral chest electrodes from 3 cm. anterior to 3 cm. posterior to the normal position did not result in consistent differences in the coefficients of variation for scalar and vector magnitudes in the two lead systems (Table II). Posterior displacement of the electrodes was associated with a slight decrease in the means for maximal QRS and T magnitudes recorded with Frank leads (10 and 15 per cent) and axial leads (12 and 10 per cent).

Mean values for scalar and vector magnitudes recorded from 70 normal Caucasian men 20 to 39 years of age were significantly smaller with Frank than with axial leads (Table III). Mean azimuths for QRS vectors were located more counterclockwise with Frank than with axial leads; the largest differences (20 to 23 degrees) were in the 0.04 second, 0.05 second, and maximal QRS vectors, and in SÂQRS. There were significant correlations between comparable variables recorded with Frank and axial leads, with correlation coefficients larger than 0.8 for 12 of the 29 variables.

There was no consistent difference between coefficients of variation computed for the same magnitude variables recorded with Frank and axial leads, or between these and comparable variables recorded with standard leads (Tables III and IV). Standard deviations for azimuth and elevation of QRS and T vectors were similar in Frank and axial lead records except for slightly smaller standard deviations for maximal QRS and SÂQRS azimuths in Frank lead records.

Frank lead data and constitutional variables in normal subjects. Means for scalar and vector magnitudes in Frank lead records were significantly smaller in normal subjects 50 to 75 years of age than in those 20 to 29 years old (Table V). Mean azimuths for the 0.02 second and 0.03 second QRS vectors in the older group were 15 and 17 degrees counterclockwise to their location in the younger group. Mean azimuths for the 0.04 second, 0.05 second, and maximal QRS and SÂQRS vectors were not significantly different in the two age groups, but these vectors were located in a more superior direction in the older group. Mean azimuth for the T vector was located slightly more anterior in the older than in the younger group.

Normal subjects 40 to 59 years of age grouped on the basis of relative body weight or anteroposterior chest diameter exhibited very small differences in means for scalar and vector magnitude measurements. However, mean azimuths for the 0.04 second, 0.05 second, and maximal QRS vectors in the groups with high relative body weight or large chest diameter were 16 to 28 degrees clockwise from their locations in the corresponding groups with low relative body weight or small chest diameter. Mean ages were not significantly different in these groups.

Multiple regression equations revealed

Table V. Frank lead measurements in groups of normal subjects separated on the basis of age and in groups 40 to 59 years of age separated on the basis of anteroposterior chest diameter

	Age					A P chest diameter		
	20-29 yr (55)		50-75 yr (97)			Small (55)	Large (45)	
	Mean	S.D	Mean	S.D	p <	Mean	Mean	p <
Age	[illegible] 56		58.10			48.16	47.56	
Ponderal index	12.71	0.43	12.43	0.53	0.001	12.82	12.27	0.001
A P chest diameter	22.16	1.69	23.65	2.01	0.001	21.52	25.98	
Scalar magnitude (mv.)								
Rx	1.09	0.36	0.84	0.28	0.001	0.76	0.93	0.005
Ry	1.01	0.37	0.57	0.32	0.001	0.71	0.61	
Sz	0.93	0.30	0.64	0.24	0.001	0.72	0.61	
Spatial magnitude (mv.)								
QRS 0.02 sec	0.40	0.17	0.28	0.12	0.001	0.30	0.29	
QRS 0.03 sec	0.61	0.19	0.60	0.20		0.58	0.64	
QRS 0.04 sec	1.31	0.34	1.04	0.30	0.001	1.07	1.09	
QRS 0.05 sec	1.51	0.46	0.88	0.34	0.001	0.97	0.89	
Maximal QRS	1.68	0.41	1.14	0.31	0.001	1.20	1.20	
SÂQRS (µv sec.)	37.8	12.0	23.8	9.7	0.001	25.6	24.4	
Maximal T	0.56	0.42	0.33	0.12	0.001	0.35	0.33	
SÂT (µv sec.)	64.3	19.4	37.2	13.9	0.001	40.7	36.00	
Azimuth (degrees)								
QRS 0.02 sec	93	19	77	33	0.001	77	82	
QRS 0.03 sec	34	29	16	26	0.001	15	21	
QRS 0.04 sec	345	22	340	30		332	350	0.005
QRS 0.05 sec	312	24	302	37		290	314	0.001
Maximal QRS	323	26	331	35		317	343	0.001
SÂQRS	311	24	316	28		313	325	
Maximal T	37	16	46	21	0.01	44	43	
SÂT	43	14	54	19	0.001	49	52	
Elevation (degrees)								
QRS 0.02 sec	−8	14	0	17	0.002	−4	−1	
QRS 0.03 sec	18	15	22	14		26	19	
QRS 0.04 sec	35	11	28	15	0.005	36	29	
QRS 0.05 sec	36	12	25	23	0.002	33	30	
Maximal QRS	36	13	28	17	0.002	37	29	0.01
SÂQRS	31	20	17	33	0.005	31	22	
Maximal T	29	8	28	13		30	24	
SÂT	−5	9	18	15	0.005	22	16	

Note: Number of subjects in each group is indicated in parentheses. Definitions of small and large chest diameter are given in the methods section. P values < 0.01 are listed.

statistically significant correlations ($p < 0.01$) between most of the variables recorded with Frank leads and a combination of age and anteroposterior chest diameter in the 305 normal subjects (Table VI). Scalar and vector magnitude measurements gave the largest correlation coefficients with constitutional variables and these could be almost entirely accounted for by age alone. Maximal QRS and SÂQRS azimuths were slightly correlated with anteroposterior chest diameter but not with age. Similar results were obtained when chest circumference was substituted for anteroposterior chest diameter. The addition of relative body weight (ponderal

Table VI Correlation coefficients for measurements of Frank lead records and constitutional variables in 305 normal subjects 20 to 75 years of age

	Age	A P chest diameter	Ponderal index	Multiple correlations	
	1	2	3	1 + 2	1 + 2 + 3
Age		0 29			
Ponderal index	−0 18	−0 31			
Scalar magnitude (mv)					
Rx	−0 28	0 05	−0 10	0 31	0 33
Ry	−0 43	−0 24	0 26	0 45	0 47
Sz	−0 38	−0 34	0 17	0 45	0 45
Spatial magnitude (mv)					
QRS 0 02 sec.	−0 30	−0 15	0 16	0 31	0 32
QRS 0.03 sec	−0 06	0 03	−0 04	0 08	0 09
QRS 0.04 sec.	−0 31	−0 16	0 09	0 32	0 32
QRS 0.05 sec	−0 51	−0 23	0 17	0 52	0 52
Maximal QRS	−0 50	−0 20	0 16	0 50	0 50
SÂQRS (mvsec.)	−0 44	−0 21	0 15	0 45	0 45
Maximal T	−0 50	−0 22	0 15	0 51	0 51
SÂT (mvsec.)	−0 52	−0 29	0 20	0 55	0 55
Azimuth (degrees)					
QRS 0 02 sec	−0 19	−0 02	−0 01	0 19	0 20
QRS 0 03 sec.	−0 [illegible]	0 07	−0 06	0 30	0 30
QRS 0 04 sec	−0 10	0 23	−0 21	0 28	0 31
QRS 0.05 sec.	−0 14	0 19	−0 17	0 27	0 29
Maximal QRS	0 07	0 28	−0 24	0 28	0 30
SÂQRS	0 03	0 24	−0 [illegible]	0 24	0 25
Maximal T	0 17	0 12	0 10	0 19	0 77
SÂT	0 23	0 12	0 09	0 25	0 32
Elevation (degrees)					
QRS 0 02 sec.	0 16	0 09	−0 09	0 17	0 17
QRS 0.03 sec	0 13	−0 20	0 25	0 27	0 31
QRS 0 04 sec.	−0 13	−0 20	0 27	0 23	0 29
QRS 0 05 sec.	−0 21	−0 12	0 15	0 22	0 24
Maximal QRS	−0 18	−0 20	0 22	0 24	0 27
SÂQRS	−0 19	−0 18	0 21	0 23	0 26
Maximal T	0 06	−0 14	0 15	0 17	0 20
SÂT	−0 12	−0 12	0 08	0 15	0 15

Note: p is <0 01 for correlation coefficients larger than 0 [illegible] with one or two independent variables and 0 18 with three independent variables in a sample of this size.

index) to the multiple regression equations produced little change in the correlation coefficients.

Discussion

This study confirmed previous observations that displacement of the horizontal level of Frank lead chest electrodes produced larger changes in amplitude of recorded data than did similar displacement of axial electrodes, and this was true for spatial as well as scalar measurements. However this finding does not indicate whether inter individual variability of data recorded with axial leads under routine clinical conditions will be less than with Frank leads. Variability of data recorded from normal subjects was found to be very similar with Frank and axial leads, and variability of scalar amplitude measurements was also similar to comparable data recorded with standard leads. The assumption that variability of data recorded with orthogonal leads should be

significantly less than that recorded with standard leads was not substantiated in this or a previous study.[13] Kaneko and associates[12] recently suggested that variability of chest electrode position relative to location of the heart may be an important factor in the wide range of the normal distribution of data recorded with corrected orthogonal leads. The failure of some recent studies to confirm the predicted superiority of corrected orthogonal leads for clinical diagnosis[4,11,18] may be related to the absence of a significant decrease in the normal distribution of data recorded with these leads as compared with standard or other noncorrected leads. The present results did not provide any basis for a preference between the two orthogonal lead systems, or between orthogonal and standard leads.

Our previous study of normal subjects demonstrated significant multiple correlations of Frank lead scalar amplitude measurements with age, relative body weight, and chest diameter, most of which could be accounted for by age alone.[8] The present study demonstrated a significant decrease in magnitude of spatial vectors associated with older age. Significant differences in azimuths of early QRS vectors and elevations of mid and maximal QRS vectors were associated with aging, while differences in azimuths of mid and maximal QRS vectors were related to body build.

Pipberger and co-workers reported a decrease in Frank lead scalar and vector magnitude measurements and a clockwise shift in azimuth of the maximal QRS vector associated with older age, heavy body weight, and relatively large anteroposterior chest diameter; there were also significant differences related to race. However, they did not indicate whether correlations with age, body build, and race were independent of each other. Silverberg[1] also observed that the maximal QRS vector was smaller and the frontal plane QRS loop was more leftward and superior in normal older subjects than in younger subjects; relationships with body build were not investigated.

Results of the present and previous studies suggest that normal limits for spatial as well as scalar magnitude measurements in orthogonal lead data should be stratified by age to provide optimum diagnostic accuracy. Although statistically significant differences in location of means for some QRS and T vectors were observed in groups separated on the basis of age and body build, the overlap in ranges for normal subjects was so large it seems doubtful that stratification of these angular measurements would improve discrimination between normal and pathological records from adult men.

Summary

Displacement of the horizontal level of chest electrodes produced larger changes in data recorded with Frank than with axial leads but anteroposterior displacement of lateral chest electrodes did not result in consistent differences between the lead systems.

Variability of data recorded from normal subjects with Frank and axial leads was very similar, so this study did not provide a basis for a selection between these lead systems.

Data recorded with Frank leads revealed smaller magnitude of QRS and T variables and a more superior location of mid and maximal QRS vectors in older normal subjects than in young subjects, while a shift in azimuth of mid and maximal QRS vectors was related to body build.

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REFERENCES

1. Pipberger, H. V.: Current status and persistent problems of electrode placement and lead systems for vectorcardiography and electrocardiography, Progr. Cardiov. Dis. [illegible]248, 1959.
2. Schmitt, O. H., and Simonson, E.: The present status of vectorcardiography, Arch. Int. Med. 96:574, 1955.
3. Frank, E.: An accurate, clinically practical

system for spatial vectorcardiography. Circulation 13:737, 1956.
4. McFee, R., and Parungao, A.: A orthogonal lead system for clinical electrocardiography. Am. Heart J. 62:93, 1961.
5. Brody, D. A., and Arzbaecher, R. C.: A comparative analysis of several corrected vector cardiographic leads, Circulation 29:533, 1964.
6. Fischmann, E. J.: Experimental comparison of parallel grid leads with simple bipolar and the SVEC III, Frank, and McFee-Parungao systems, Am. Heart J. 70:627, 1965.
7. Simonson, E., Horibe, H., Okamoto, N., and Schmitt, O. H.: Effect of electrode displacement on orthogonal leads, in Hoffman, I., and Taymor, R. C., editors: Vectorcardiography 1965, Amsterdam, 1966, North-Holland Publishing Company, pp. 38-46.
8. Borun, E. R., Chapman, J. M., and Massey, F. J., Jr.: Electrocardiographic data recorded with Frank leads in subjects without cardiac disease and those with left ventricular overload, Am. J. Cardiol. 18:656, 1966.
9. Borun, E. R., Chapman, J. M., and Massey, F. R., Jr.: Computer analysis of Frank lead electrocardiographic data recorded in an epidemiological study. Am. J. Cardiol. 18:664, 1966.
10. Pipberger, H. V.: Computer analysis of the electrocardiogram, in Stacy, R. W., and Waxman, B. C., Editors: Computers in biomedical research, New York, 1965, Academic Press, Inc. Vol. 1, Chapter 16.
11. Downs, T. D., Liebman, J., Agusti, R., and Romberg, H. C.: The statistical treatment of angular data in vectorcardiography, in Hoffman, I., and Taymor, R. C., Editors: Vectorcardiography 1965, Amsterdam, 1966, North-Holland Publishing Company, pp. 272-278.
12. Caceres, C. A., Rosner, S. W., Sherman, D., Abraham, S., and Weihrer, A. L.: Concepts in electrocardiographic processing, in Hoffman, I., and Taymor, R. C., Editors: Vectorcardiography 1965, Amsterdam, 1966, North-Holland Publishing Company, pp. 382-388.
13. Kaneko, K., Simonson, E., and Schmitt, O. H.: Relationship between the position of chest electrodes (Frank and SVEC III systems) and the anatomic position of the heart. Am. Heart J. 1:58, 1967.
14. Tannenbaum, O., Vesell, H., and Schack, J. A.: A simple corrected orthogonal lead system of electrocardiography: Correlation with the conventional twelve lead electrocardiogram and clinical information, Am. Heart J. 65:349, 1963.
15. Simonson, E., Tuna, N., Okamoto, N., and Toshima, H.: The diagnostic value of the electrocardiogram and of the vectorcardiogram. A cooperative study. Am. J. Cardiol. 1:829, 1966.
16. Morse, R. L., Wolff, L., and Wolff, R.: Frank system versus double cube in left ventricular hypertrophy, in Hoffman, I., and Taymor, R. C., Editors: Vectorcardiography 1965, Amsterdam, 1966, North-Holland Publishing Company, pp. 23-25.
17. Pipberger, H. V., Goldman, M. J., Littman, D., Murphy, G. P., Cosma, J., and Snyder, J. R.: Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men, Circulation 35:536, 1967.
18. Silverberg, S. M.: A quantitative study of the Frank vectorcardiogram. A comparison of younger and older normal populations, Am. J. Cardiol. 18:672, 1966.

Left ventricular ejection period

Measurement by atraumatic techniques: Results in normal young men and comparison of methods of calculation

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The left ventricular ejection period is an important parameter of cardiac performance. Ejection occurs between opening and closing of the aortic valve, coinciding with the interval from the beginning of the upstroke of the central aortic pulse to the nadir of its incisura. It has been shown that ejection times can be measured from analogous points on the externally recorded carotid sphygmogram and that values so obtained differ negligibly from those directly taken from the aortic curve.[1-4] Moreover, it has been proposed that the ejection period can also be derived from a combination of the apex cardiogram (ACG) and the externally recorded phonocardiogram (PCG). If the ACG-PCG derived ejection time measurement is accurate, it would have advantage not only as a cross-check on other methods but also for measurements when a technically good carotid curve is not available.

It is our purpose (1) to report results in normal young adult male subjects, (2) to compare these results with those obtained by others, and (3) to compare carotid-derived ejection times with those obtained by us from the ACG and PCG.

Material and methods

A total of 50 normal young men, 21 to 35 years of age, were studied by means of simultaneous ACG, PCG, and carotid sphygmogram. All subjects fulfilled strict criteria for inclusion: (1) no history of heart disease, suspected heart disease, suspected rheumatic fever, or known murmurs; (2) normal physical examination; (3) normal 12 lead electrocardiogram (ECG); (4) normal chest roentgenogram; (5) normal activity status—so-called hospital normals were excluded.

With the subject resting in the semileft decubitus and in expiratory apnea, recordings were made at 75 mm. per second with time lines 40 msec. on a Sanborn 8-channel photographic recorder. The Sanborn dynamic microphone and piezo-electric ACG apparatus was used for simultaneous ACG and apical PCG and a Sanborn No. TPS-10

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Fig. 1 Methods of measuring LVET. The bracket and "LVET" indicates method (1). Carotid upstroke to incisura. The arrow indicates the assumed "true E" point of method (4).

pulse transducer for recording the right carotid sphygmogram.

Fig. 1 illustrates methods of measuring left ventricular ejection time (LVET). Ejection time (EjT) was measured from the beginning of the carotid upstroke (u) to the nadir of the carotid incisura (In)

$$E_jT = \quad - In, \qquad (1)$$

and from the maximal systolic peak (E) of the ACG to the end of ejection as reflected by the aortic component of the second heart sound (II_A)

$$EjT = E - II_A \qquad (2)$$

Since the E-point usually *follows* rather than marks, the actual onset of ejection (v.i.) additional calculations were made to account for this delay. An attempt was made to approximate this by subtracting the carotid delay time ($II_A - In$)

$$EjT = (E \text{ minus carotid delay}) - II_A \qquad (3)$$

In 42 subjects showing a distinct notch on the ACG upstroke shortly before E, this point was used instead of E, since it has been held to represent the true ejection onset.[4,8]

$$EjT = \text{"true E"} - II_A \qquad (4)$$

Measurements were made over four consecutive cardiac cycles and expressed to the nearest 10 msec.

Results

The composite results are listed in Table I. Ejection time calculated from the carotid curves—method (1)—gave a range of 240 to 320 msec., mean = 292 ± 19 msec. Methods (2), (3), and (4) showed similar mean values, particularly (3) and (4) in which the correction factors were applied, but there was much more scatter and correlation with method (1) was poor (correlation coefficients r = 0.502, 0.676, and 0.5.5 respectively.)

Fig. 2 shows the close linear relationship of carotid-derived EjT to heart rate. Our regression equation for this is 0.376 − 0.122HR (r = 0.8, P < 0.01). Fig. 3 compares the regression line of results with those obtained by Weissler and associates[1] and Morbelli and co-workers.[6]

Discussion

Ejection time values obtained in our series were very close to those found in normal subjects by other investigators. Our regression line (Fig. 3) was virtually identical over the range of heart rates studied with that of Morbelli and co-workers[6] and agreed extremely well with that of Weissler and associates.[1]

Methods of estimating ejection time from ACG + PCG, while yielding somewhat similar mean values, showed poor correlation with the carotid-derived time (Table I, columns 2, 3, and 4). Since ejection times measured from central aortic curves are negligibly different from those obtained from external carotid curves, the latter can safely be considered the standard for external measurements. Our results indicate that methods using apexcardiography are not dependable because of their frequent divergence from this standard. The reasons for this divergence are probably related to the difficulty of defining a point on the ACG curve which reliably reflects the beginning of ejection.

It has been held that the maximal systolic peak (E) of the ACG marks the onset of ejection.[10] We have observed that the E-crest most often either coincides with the beginning of the carotid upstroke

Table I. Left ventricular ejection period

Method	Results of calculation by different methods			
	(1) – I	(2) E – II	(3) (E-CAR. delay)	(4) true E' – II_A
No. of subject	50	50	50	42
Range (msec.)	240 to 320	120 to 330	160 to 350	250 to 350
Mean	292	267	291	295
S.D. (±)	19	35	29	34
Correlation with method (1) =	–	0.502	0.676	0.525

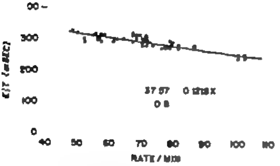

Fig. 2. Relationship of LVET to heart rate. Note the regression equation depicted is in centiseconds; for milliseconds this should read: 375.7 – 1.22 HR (simplified 376 – 1.2 HR).

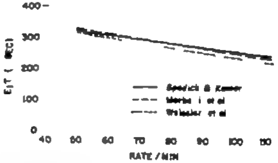

Fig. 3. Comparison of results of LVET in this series with those of other investigators for carotid-derived measurement.

(u) or follows it by a short interval. Hence E must occur after ejection commences in the great majority of individuals. Moreover, Tavel and associates recorded the central aortic pulse and the ACG in nine patients and found that E did indeed follow the onset of ejection by 37 ± 26 msec. Therefore, since II reliably marks the end of ejection, the calculation EjT = E – II_A should understate the actual ejection period, as it did in our observations (Table I).

Elsewhere it is the practice to subtract the carotid delay time from E as an expression of mechanical delay; in our subjects this yielded a similar mean value but had an inadequate correlation with the carotid-derived ejection times (r = 0.676). This may be explained by either the impropriety of applying the carotid delay to a different curve or to the ambiguity of an exact E point in a curve which sometimes has a broad summit—or both. Attempts to use the assumed "real E" notch [4] on the ACG upstroke gave worse results (r = 0.525). This notch probably represents vibrations of the first heart sound which are unrelated to ejection.

Summary

1. Left ventricular ejection periods were measured by several methods in 50 normal active young adult men.

2. The carotid-derived ejection times yielded a range of 240 to 320 msec. (mean 292 ± 19 msec. S.D.) over 48 to 102 beats per minute heart rate. Our regression equation for the relationship of LVET to heart rate in beats per minute is: LVET = 376 – 1.22 HR.

3. Ejection times were linearly inversely proportional to heart rate. The line expressing this relationship agreed very closely with those of other investigators.

4 Ejection times calculated from ACG PCG data, even when corrected did not reliably correlate with carotid-derived ejection times, which must be regarded as the standard for external methods.

REFERENCES

1 Wessler A. M Peeler R. G nd Roehll, W H J : Relationships between left ventricular ejection time, stroke volume, and heart rate i normal individuals and patients with cardiovascular disease, Am HEART J 62:367 1961

2 Morbelli, E Mevcaretti, L., and Giura, R. I fattori che regolano la durata della eseziore ventricolare nell'uomo, Folia Cardiol. 24:123 1965.

3 Margolis, C. The significance of ejection period/tension period as factor in the assessment of cardiac function and as a possible diagnostic tool for the uncovering of silent coronary disease, Dis. Chest 46 706, 1964

4. Agress, C. M Wegner S., Nakakura, S., Lehman, E. H., and Chait, L. Comparison of the ejection time-heart rate relationships in normal and ischemic subjects, Jap. Heart J 6:496, 1965.

5. Scott, R. Clinical assessment of left bundle branch block, Am. HEAR J 70:690, 1965

6. Oreshkov V Indirect measurement of isovolumetric contraction time on the basis of polygraphic tracing, Cardiologia 4 :315 1965

7 Raineri, A. Il ardiogramma picale nella valutazione della dinamica cardiaca, Boll Soc. Ital. Cardiol. 10:64 1965

8. Dallocchio, M Bricaud, H Drouet, B., Bonavita, J P and Broustet, P Étude comparative du cardiogramme apexien et des traces de pression intra ventriculaire gauche, Arch mal. Coeur 58:1078, 1965.

9 Bench mol, A., and Dimond, E. G. The normal and bnormal apex cardiogram, Am J Cardiol. 12:368, 1963

10. Warembourg H and Ducloux, G L pexogramme pplication à l'étude des cardiopathies mitrales, Arch. mal. Coeur 56 1359 1963

11 Benchimol, A., Wu, T L., and Dimond, E. G Apex cardiogram in the diagnosis of congenital heart disease, Am J Cardiol. 17:63, 1966.

12. Martinez-Lopez, J L Clinical application of the pex cardiogram, South. M J 58 1197 1965

13. Lohr H. A., van Vollenhoven, E., and van Rotterdam A. Fundamentals i vibrocardiography precordial accelerography and acceleration ballistocardiography Am. HEART J 66:108, 1963

14 T vel, M. E., Cambell, R. W Feigenbaum H and Steinmetz, E. F The apex cardiogram and its relationship t haemodynamic events within the left heart, Brit Heart J 27:829 1965

Effects of iproveratril and nitroglycerin in the heart and coronary circulation of dogs

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Although iproveratril (α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile, Isoptin®) has been shown to increase coronary flow in animals[1-3] and has been used successfully in the treatment of angina pectoris,[4] information concerning some of its cardiovascular actions is incomplete. For example, there have been no direct measurements of the effect of the agent on instantaneous coronary inflow, myocardial contractile force, or cardiac output in the intact animal. In the present study, noncannulating electromagnetic flowmeters were used to measure blood flow in the ascending aorta and coronary arteries of anesthetized open-chest dogs. Myocardial contractile force was determined by a Walton-Brodie strain-gauge arch. The effects of both intracoronary and intravenous iproveratril were observed and were compared with those of nitroglycerin.

Methods

Ten dogs weighing 15 to 25 kilograms were anesthetized with 30 mg. per kilogram of intravenous pentobarbital sodium. Polyethylene catheters were placed in an external jugular vein and a common carotid artery for intravenous injections and systemic arterial pressure measurements, respectively. A lateral thoracotomy through the fourth left intercostal space was performed, ventilation being maintained by a Bird Mark 8 respirator. The pericardium was incised and the aorta was cleared of fat and connective tissue. A convenient branch-free segment of the anterior descending coronary artery about 1 cm. in length was dissected free from the epicardium. Noncannulating electromagnetic probes were placed on these vessels and a strain-gauge arch was sutured to the anterior left ventricular myocardium between the interventricular groove and the apex. Flow was measured with 400 c.p.s. gated sine-wave flowmeters.[7] The zero reference for coronary flow was obtained by means of a snare placed downstream from the coronary flow probe. The absence of interference between the aortic and coronary probes was confirmed by observing the output of one while turning off the magnet current of the other. Calibration was performed by allowing saline to pass from a gravity-feed reservoir through the lumen of the probe into a graduate. No arterial wall was used. The validity of this method of calibration has been pre-

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viously demonstrated by others.[8] Systemic arterial pressure was measured with a Sanborn 267B transducer. Intracoronary injections were made downstream from the flow probe through an indwelling 25 gauge needle connected by polyethylene tubing to a microsyringe. Iproveratril was administered in the form of its hydrochloride (Isoptin HCl) and doses are expressed in terms of this salt.

Results

Intracoronary injections. Nitroglycerin 4 to 40 μg injected into the anterior descending coronary artery increased flow in this vessel. The response began within 2 to 4 seconds, reached a peak in 8 to 12 seconds, and returned to control values in less than 30 seconds (Fig. 1, *A*). Both systolic and diastolic flow increased and the end-diastolic pressure/flow ratio diminished. There was no change in arterial pressure, heart rate, or the relative durations of systole or diastole. Intracoronary iproveratril 4 to 40 μg produced similar changes except that the duration of the coronary flow increase was considerably more prolonged and lasted 1 to 8 minutes (Fig. 1, *B*).

Intravenous injections. Intravenous nitroglycerin 1 to 10 μg per kilogram reduced systemic arterial pressure and produced a biphasic coronary flow response consisting of an initial brief increase followed by a more prolonged decrease which paralleled the fall in arterial pressure (Fig. 2, *B*). The instantaneous coronary flow changes during the period of increased flow were identical to those which followed intracoronary nitroglycerin (Fig. 3, *B*). During the period of decreased flow both systolic and diastolic flow decreased and

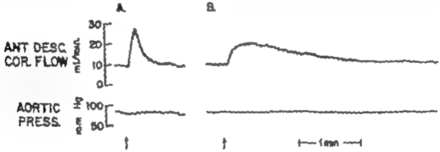

Fig. 1. Effects of intracoronary nitroglycerin and iproveratril on coronary blood flow. Upper trace, mean flow in the left anterior descending coronary artery. Lower trace, mean aortic pressure. *A*, Nitroglycerin, 40 μg. *B*, Iproveratril, 40 μg.

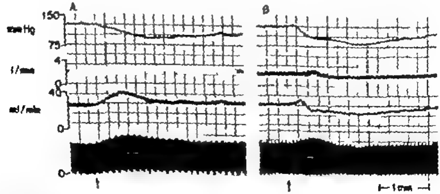

Fig. 2. Effects of intravenous iproveratril and nitroglycerin on (from top to bottom) systemic arterial pressure, cardiac output, anterior descending coronary flow, and myocardial contractile force. *A*, Iproveratril, 0.1 mg per kilogram. *B*, Nitroglycerin, 5 μg per kilogram.

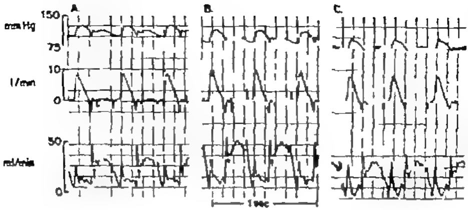

Fig. 3. Effects of intravenous nitroglycerin, 5 μg per kilogram, on systemic arterial pressure (upper trace), instantaneous aortic flow (middle trace), and instantaneous flow in the anterior descending coronary artery. *A*, Control. *B*, At maximum coronary flow. *C*, At maximum hypotension.

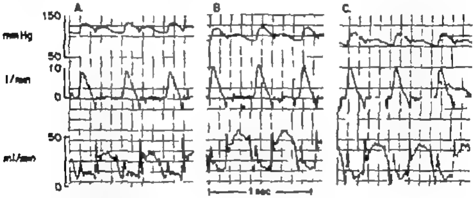

Fig. 4. Effect of intravenous iproveratril, 0.1 mg. per kilogram, on systemic arterial pressure (upper trace), instantaneous aortic flow (middle trace), and instantaneous flow in the anterior descending coronary artery. *A*, Control. *B*, At maximum coronary flow. *C*, At maximum hypotension.

systolic backflow was frequently observed (Fig. 3, *C*). Heart rate did not change significantly. *Cardiac output and contractile force* increased during the first minute of the response and then fell to preinjection levels. In some dogs a biphasic response was seen and, following the initial increase, both cardiac output and contractile force fell below preinjection levels before returning to normal values 3 to 6 minutes after injection (Figs. 2, *B* and 3). *The effects of iproveratril* (50 to 125 μg per kilogram) differed from those of nitroglycerin in that coronary flow was increased throughout the period of hypotension (Fig. 4). In no case was a reduction in coronary flow observed. Initially both systolic and diastolic coronary flow increased (Fig. 4, *B*) but subsequently systolic flow returned to control values *so that the increased coronary flow during* the later stages of the response was solely due to increased diastolic flow (Fig. 4, *C*). The duration of the arterial pressure and coronary flow responses was 3 to 4 times longer than those induced by nitroglycerin. Contractile force changes were small and resembled those produced by nitroglycerin. Cardiac output increased slightly throughout the response (Figs. 2, 4, and 4). No significant changes in the heart rate were observed with either nitroglycerin or iproveratril.

The quantitative changes produced by these agents in the *variables studied are* shown in Table I.

Table I. Maximum mean per cent changes (± standard errors) produced in several hemodynamic variables by intravenous nitroglycerin 5 μg per kilogram and by intravenous iproveratril 0.1 mg per kilogram. Note that nitroglycerin produced biphasic responses in coronary flow and cardiac output

	Nitroglycerin		*Iproveratril*	
	Per cent change	*No. of animals*	*Per cent change*	*No. of animals*
Heart rate	0	7	[illegible]	10
Systemic arterial pressure	−25 ± 5	7	−18 ± 2	10
Coronary blood flow	+51 ± 8 −26 ± 8	6	+75 ± 10	10
Cardiac output	+ 5 ± 5 −13 ± 6	5	+11 ± 4	6
Contractile force	+14 ± 4	6	+9 ± 5	6

Discussion

The present study confirms previous observations that iproveratril increases total coronary blood flow.[2] Examination of instantaneous flow records following intracoronary injection of this agent shows that both systolic and diastolic coronary flow increase. Since aortic pressure and heart rate and the relative durations of systole and diastole do not change, the increased coronary flow must be due to a dilatation of the coronary resistance vessels. This effect also occurs when iproveratril is given intravenously and coronary flow increases despite a concurrent reduction in arterial pressure. Since cardiac output is slightly increased, the hypotensive effect of iproveratril must be due to a reduction in total peripheral vascular resistance as previously shown in the cat. The increase in coronary flow induced by intracoronary and intravenous nitroglycerin is of much shorter duration than that produced by iproveratril. Moreover, the systemic hypotensive effect of nitroglycerin is only partly due to peripheral vasodilation since cardiac output after a short initial increase tends to be reduced (Fig. 2). The reduction in output may be due partly to a venous pooling effect[14] and in some cases to a reduction in myocardial contractile force in the later stages of the response (Fig. 2).

Iproveratril has been shown to have a negative inotropic effect in cat papillary muscle[8] and in the isolated perfused rabbit heart. These observations are in contrast with those of the present in vivo study in which iproveratril increased myocardial contractile force. The increase persisted throughout the response in some animals but in others a slight reduction in contractile force followed the early increase. Nitroglycerin also transiently increased contractile force. Darby and associates[12] have reported that this effect is abolished by sympathectomy. They suggested that the increased myocardial force was caused by sympathetic activity reflexly induced by the fall in arterial pressure. A similar mechanism may well account for the positive inotropic effect of iproveratril observed in our animals.

In these studies, iproveratril produced substantial increases in coronary blood flow. Moreover, this effect was of longer duration than that produced by nitroglycerin. However, the apparent success of iproveratril in the treatment of angina pectoris[3-6] may not depend on its ability to dilate the coronary vessels. Luebs and associates,[13] using an isotope method, showed that both nitroglycerin (0.8 mg sublingually) and iproveratril (5 mg intravenously) increased coronary flow in normal individuals, but not in patients with ischemic heart disease. Mignault,[4] using coronary cineangiography, found no evi-

dence of coronary dilatation after iproveratril administration in patients with either normal or diseased coronary arteries, whereas coronary dilatation can be demonstrated by this technique after administration of nitroglycerin.[15] Melville and Benfey[11] reported that iproveratril had a β-adrenergic blocking effect on isolated heart muscle preparations and Mignault[14] suggested that this action may be responsible for its beneficial effect in angina. This seems unlikely since the conventional β-adrenergic blocking agents produce striking reductions in myocardial contractile force[16] and such changes were not observed in our animals. In earlier work on cats we were unable to demonstrate any effect of iproveratril in blocking the actions of subsequently administered isoproterenol. The basis for the therapeutic action of this agent, like that of nitroglycerin, therefore remains obscure.

REFERENCES

1. Schlepper, M., and Witzleb, E.: Tierexperimentelle Untersuchungen über die Veränderungen von Coronardurchblutung und Sauerstoffverbrauch des Herzens nach α-Isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitril, Arzneimittel-Forsch. 12:559, 1962.
2. Haas, H., and Hartfelder, G.: α-Isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitril, eine Substanz mit coronargefässerweiternden Eigenschaften, Arzneimittel-Forsch. 12:549, 1962.
3. Tschirdewahn, B., and Klepzig, H.: Klinische Untersuchung über die Wirkung von Isoptin und Isoptin S bei Patienten mit Koronarinsuffizienz, Deutsch. med. Wchnschr. 88:1702, 1963.
4. Kooch, G., Schlepper, M., and Witzleb, E.: Untersuchungen an Gesunden und Koronarkranken Patienten mit Isoptin, Med. Klin. 58:1485, 1963.
5. Neumann, M., and Luisada, A. A.: Double blind evaluation of orally administered iproveratril in patients with angina pectoris, Am. J. M. Sc. 251:552, 1966.
6. Pezzo, G., Brina, A., and Barbera, G.: Trattamento delle coronaropatie: studio di un nuovo farmaco, l'iproveratril, Min. Med. 57:3341, 1966.
7. Kolin, A., and Kado, R. T.: Miniaturization of the electromagnetic blood flowmeter and its use for the recording of circulatory responses of conscious dogs to sensory stimuli, Proc. Nat. Acad. Sc. 45:1312, 1959.
8. Gregg, D. E., Khouri, E. M., and Rayford, C. R.: Systemic and coronary energetics in the resting unanesthetized dog, Circulation Res. 16:102, 1965.
9. Ross, G., and Jorgensen, C. R.: Cardiovascular actions of iproveratril, J. Pharmacol. & Exper. Therap. In press.
10. Case, R. B., and Roven, R. B.: Some considerations of coronary flow, Progr. Cardiovas. Dis. 6:45, 1963.
11. Melville, K. I., and Benfey, B. G.: Coronary vasodilator and cardiac adrenergic blocking effects of iproveratril, Canad. J. Physiol. & Pharmacol. 43:339, 1965.
12. Darby, T. D., Sprouse, J. H., and Walton, R. P.: Evaluation of sympathetic reflex effects on the inotropic action of nitroglycerin, quinidine, papaverine, aminophylline, and isoproterenol, J. Pharmacol. & Exper. Therap. 122:386, 1958.
13. Loeb, E. D., Cohen, A., Zaleski, E. J., and Bing, R. J.: Effect of nitroglycerin, intensain, isoptin, and papaverine on coronary blood flow in man, Am. J. Cardiol. 17:535, 1966.
14. Mignault, J. de L.: Coronary cineangiographic study of intravenously administered isoptin, Canad. M. A. J. 95:1252, 1966.
15. Gensini, G. G.: Coronary angiography, Progr. Cardiovas. Dis. 6:155, 1963.
16. Nakano, J., and Kusakari, T.: Effect of beta adrenergic blockade on the cardiovascular dynamics, Am. J. Physiol. 210:833, 1966.

Vasa vasorum of the heart

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Despite the evident importance of blood supply to any tissue and the critical importance of the coronary vascular system to the body as a whole, few investigations have been concerned with the blood supply to coronary vessels. It has been suggested that disorders of this subgross vascular bed of the arterial wall may contribute to development of atherosclerosis[1] as well as occlusive complications of it.[1-4] During the past few years several investigators have discussed lymphatics of the heart,[5-8] and James[9] has written extensively on the anatomy of the coronary circulation, but not since the classical studies of Wintersitz and associates[1] in the 1930's has a systematic description of vasa vasorum of coronary arteries been undertaken. The observations of human and swine hearts reported here were made with the aim of applying modern techniques to the delineation of the anatomy of nutrient vascular beds of coronary arteries, veins, nerves and lymphatics.

Methods and materials

Studies in swine have shown that their cardiovascular systems are similar to those in man, and in aged swine atherosclerotic lesions develop that resemble those seen in man. For these reasons hearts from healthy pigs approximately six months of age were obtained from a local abattoir and studied in an effort to define normal vascular patterns. The approximate age ratio in years of swine to man is 5:1.[10]

A total of 30 hearts were obtained at autopsies from patients who had died from various causes. A total of 17 were from male patients between 3 months and 72 years of age, and 13 from female patients between the ages of 10 months and 84 years. Since only three patients in the series were under the age of 40 years, a normal human series could not be obtained.

Vasa were demonstrated by injection, clearing, and stereomicroscopic dissection. Several injection masses were tried in an effort to find substances capable of entering the smallest vessels without filtering through their walls and containing stable pigments that would contrast with surrounding tissues without staining them. Of the several materials used, only India ink 1:8 aqueous suspension, lead chromate, and General Electric's red RTV 20†[11] (a room temperature vulcanizing silicone rubber) were satisfactory. High viscosity of

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various latex compounds and other RTV compounds prevented their entering small vessels adequately. Microcrystalline barium sulfate (Microtrast) could be made to enter capillaries satisfactorily but caused clouding of specimens and the solution in which the dissection was being done when it escaped from vessels ruptured during injection or dissection. Precipitation of lead chromate within vessels by injection of lead acetate and potassium dichromate was used by Williams, but we preferred to precipitate the lead chromate, suspend the particles by vigorous agitation, and then inject promptly. This resulted in good filling of small vessels and capillaries and the bright yellow color contrasted well with India ink and red RTV 201. Silver chromate precipitate formed by combining silver nitrate and potassium dichromate was tried but the maroon color did not contrast well with surrounding tissues.

The left anterior descending coronary artery and vein were selected for study. One cannula was inserted into the artery through the coronary ostium and another into the venous system via the coronary sinus. Sutures were tied tightly around the cannulas and 50 to 100 ml. of mass injected simultaneously through each with standard Luer lok syringes. Masses of contrasting color were injected into the respective cannulas in an attempt to distinguish vessels of arterial origin from those of the venous system. In several specimens in which blood vessels were not injected, lymphatic channels demonstrated by topical application of hydrogen peroxide were injected directly with India ink from a syringe through a small gauge needle.

Pulsatile injections with pressures approximating normal arterial values were tried as well as nonpulsatile injection by gravity from a reservoir 2 or 3 feet above the specimen and uncalibrated hand pressure on a syringe containing the mass. No significant differences in results obtained by the three methods could be defined and the direct approach with the syringe was used in nearly all preparations reported here.

After injection, a portion of the myocardium was excised with coronary artery and vein intact, fixed in 10 per cent formalin, dehydrated, and cleared by a modification of the Spalteholz method.[1] Phenylethylene (styrene) was found to produce very rapid clearing but proved to be unsuitable because of spontaneous polymerization after about two weeks.[B] Methylsalicylate, though acting more slowly than styrene, was the best clearing agent and permitted indefinite storage of specimens for subsequent study. Glycerin required longer clearing time than methyl salicylate and was less consistent in its degree of clearing, probably because of the size and thickness of the specimen. Cleared specimens were submerged beneath the clearing agent in a shallow dish and dissected under stereomicroscopic observation with the perivascular structures being maintained in their normal anatomic relationships. Findings were photographed with an Exacta reflex camera back attached to one ocular of the stereomicroscope and exposure time was determined by means of a photometer attached to the other ocular. The light source for photography and dissection was a 35 mm. slide projector with a 500 watt bulb.

Results

Pig hearts. Some injections are unpredictably less effective than others, but generally *it is possible to demonstrate the vasa of* arteries, veins, lymphatics, and nerves satisfactorily. It is not uncommon to see venous injection mass in arterial channels and vice versa, and often both masses are found in the same vessel so that the decision as to whether small channels should be classified as venous or arterial is arbitrary. Thickening of arterial walls, thrombosis, intramural hemorrhage, or other evidence of atherosclerosis was not found in any of these hearts.

Vasa in the adventitia of coronary arteries and their larger branches are derived from primary, secondary, and smaller branches of the artery and vein. The greatest number of vasa are on the lateral aspects of the arteries (20 to 40μ in width) with transverse communications across the subepicardial surface. At the adventitial medial junction, capillaries course

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Fig 1 A view of the subepicardial surface of a coronary artery from pig illustrating superficial and deep adventitial vasa vasorum The longitudinal axis of the artery extends from left to right of the photograph. Predominance of superficial vasa (20 to 40 μ in width) along the lateral aspects of the artery with transverse communications are shown In the deep adventitia smaller vasa (5 to 7 μ in width) are seen coursing along the longitudinal axis of the coronary artery wall (see text) (×30.)

longitudinally and form a network but do not penetrate into the media. They derive from ramifications of superficial adventitial vasa or directly from small branches of the coronary artery which as they leave the main artery give off a branch at the junction of media and adventitia These capillaries (5 to 7 μ in width) often contained both injection masses and could be removed easily by stripping the adventitia with a small probe (Fig 1)

By dissection from beneath the main vessels are approached from their myocardial surface and from this aspect the arrangement of the vasa differs slightly in some respects from that on the subepicardial surface though their origins are identical. Transverse communicating vessels between vasa of the lateral aspects of the arteries are not seen in the adventitia of the myocardial aspects The vasa here consist of venules and arterioles oriented along the longitudinal axis of the coronary artery with frequent ramifications to the adventitial medial junction where capillary networks form similarly to those on the subepicardial surface

Vasa of coronary veins differ significantly from those of arteries though arising from the same sources. In general venules and arterioles course longitudinally in relation to the underlying vein and numerous capillaries (5 to 7 μ in width) extend from them forming an intricate network penetrating deeply into the media but not communicating with the vein lumen The vasa are distributed equally in the subepicardial and myocardial aspects of the vein wall (Fig 2)

Injection masses introduced into the coronary arteries and or veins often appear promptly in lymphatic channels (Figs. 3 and 4) Lymphatic collecting ducts and plexuses of subepicardial lymphatic capillaries fill from the apex of the heart toward the base, though injection masses are introduced near the base Arterial mass appears in lymphatics more frequently than venous mass and occasionally both are seen in the same lymph channel but ink injected directly into larger lymphatic ducts appears in veins and not in arteries. Lymphatics are identified morphologically by their thin walls, irregular contour and meandering course. The larger channels (1 to 3 mm in width) accompanying the coronary arteries and veins course toward the atrioventricular sulcus from whence

Fig. 2. Vasa vasorum of coronary vein from pig. The epicardium has been removed and perivascular tissue has been dissected away. The longitudinal axis of the vein extends from left to right of the photograph. The vasa illustrated (5 to 7 µ in width) are in the deep adventitia and penetrate the wall of the vein. The relatively avascular strands coursing generally longitudinally along the vein wall are nerve fibers. The vasa nervorum are seen as small parallel vessels in the lateral margins of these structures (see text). (×30.)

Fig. 3. Lymphatic capillary plexus near the apex and lymphatic collecting duct that has filled after injection of lead chromate into the left anterior descending coronary artery of pig heart. The coronary artery is seen near the left margin of the heart in the photograph (see text).

the main cardiac lymph duct arises.[7,9] Anatomical communications between blood vessels and lymphatics were not identified.

The vasa of lymphatic ducts (vasa vasorum lymphorum) derive from sources in common with those of the coronary arteries and veins, and are distributed similarly to vasa of veins. The depth of penetration if any of these vasa could not be determined and communication with the lumen of lymphatic vessels was not identified (Fig. 5).

The intraneural vasculature of subepicardial nerves is demonstrated in nearly all specimens concomitantly with vasa of coronary arteries and veins. Many nerve trunks (750 to 1,000 µ in width) are distributed over the subepicardium with numerous smaller branches (40 to 250 µ in width) penetrating into the myocardium and perivascular tissue. Many of these smaller branches are seen at the adventitial medial junction of arteries and veins. Usually one of the larger nerve trunks accompanies the blood vessels either between the artery and vein or close to one side (Fig. 6).

The small blood vessels supplying nerves

Fig. 4 Lymphatic ducts filled with arterial injection mass in pig heart that has been cleared. The coronary artery and its vasa are seen toward the left of the illustration and the vein is to the right of the artery. Vasa vasorum lymphorum are prominent in the lymph channel to the left of the artery (see Fig. 3). (X7.)

are derived from regional sources in common with the vasa of blood vessels and lymphatics. Branches of these small vessels run parallel in the epineurium along the longitudinal axis of the nerves and there is no apparent pattern to their frequent entry into and exit from the epineurium. Arteries and veins sometimes accompany each other and sometimes appear singly. Arterioles and venules from the epineural vessels penetrate the nerves transversely giving off smaller branches (10 to 20 μ in width) which course longitudinally in a tortuous manner and anastomose freely to form a characteristic interwoven pattern (Figs. 6 and 7). Histological sections showed these vessels in the perineurium between the neural fasciculi. This pattern of vasa nervorum is similar to that described by others in nerves of the extremities.[16-18] Unequivocal identification of nerves can be made by the unique characteristic of their vascular pattern though small nerve branches (40 to 250 μ in width) entering perivascular tissue are usually accompanied by only a pair of parallel vessels in the epineurium (Fig.). In uninjected cleared specimens, nerves are identified as thin solid translucent structures with tensile strength much greater than that of blood vessels or lymphatics of comparable size.

Human hearts. The changes of atherosclerosis in the coronary arteries were apparent grossly and microscopically in all human specimens examined except those from two infants under one year of age. In many intramural hemorrhage and calcification were present. Intramural hemorrhage was identified as reddish brown deposits of acid hematin resulting from a chemical reaction between hemoglobin and formalin.[19] Changes of atherosclerosis made clearing of human specimens less satisfactory than that of young pigs, and in a number of instances intramural hemorrhages were recognized only by examination of cross sections. In none of the specimens examined was there complete occlusion of an arterial lumen by thrombosis, atheroma or intramural hematoma.

Superficial adventitial vasculature about human coronary arteries is similar to that observed in pigs. Deep adventitial vasa are more dense in humans than in pigs and adventitial capillaries penetrating into thickened media form plexuses which are joined frequently by vasa arising directly from the arterial lumen. These collections of vessels are particularly dense about areas of calcification and intramural hemorrhage (Figs. 8 and 9). Identification of intramural

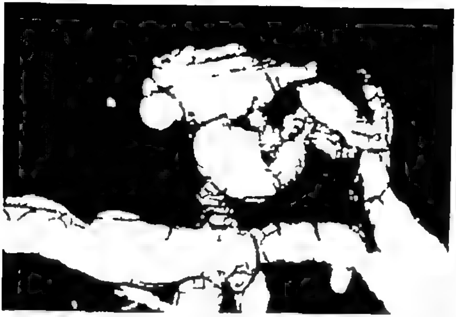

Fig. 5. L[illegible]mphatic duct [illegible] pig heart filled with microcry[illegible]talline barium sulf[illegible] that was injected int[illegible] the coronary artery. [illegible] va[illegible] vasorum lymphorum contain India ink injected int[illegible] the coronary [illegible]ein. The absence of ink in the barium suggests that these [illegible]asa do not comm[illegible]icat[illegible] with the lumen of the underlying lymphatic [illegible]hannel. (×30.)

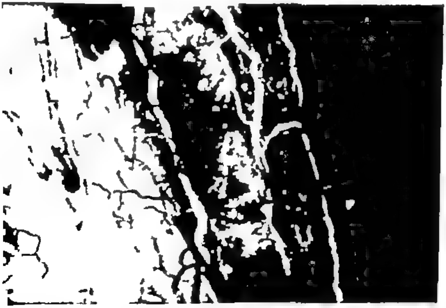

Fig. 6. Three [illegible]tructures frequentl[illegible] seen i[illegible] p[illegible] heart. At the left of the photogr[illegible]ph the [illegible] [illegible]pearing are [illegible] coronary artery wall with [illegible]uperf[illegible]ial [illegible] deep ad[illegible]ent[illegible]tial [illegible]a[illegible] [illegible]sorum. To the right of the [illegible]enter is the typical intera[illegible] pattern of [illegible] a nerv[illegible]rum with thin [illegible]ner[illegible] trunk. Bet[illegible]een these t[illegible] [illegible]truct[illegible]res and [illegible]lightly broader than the nerv[illegible] is [illegible] paracoronary lymph duct [illegible]onta[illegible]ing arterial inject[illegible]on mass [illegible]hich ha[illegible] fl[illegible]culated [illegible]lightly. The [illegible]ein is t[illegible] the [illegible]ght of these [illegible]tructures b[illegible]t [illegible] not included in the ill[illegible]tr[illegible]tion. (×5.)

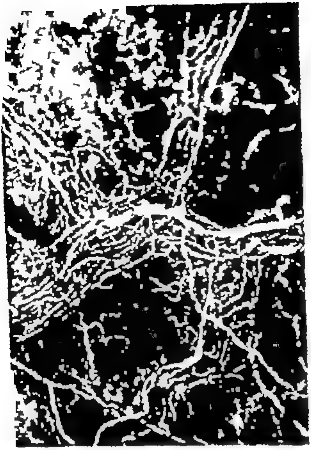

Fig. 7. Nerve plexus in pig heart injected with RTV 201 illustrating the interwoven pattern of vasa nervorum. Several nerve branches are seen emanating from the main trunk which extends from left to right of the photograph. (×25.)

Fig. 8. Vasa vasorum about an area of calcification in the coronary artery wall of a human. The calcific deposits which would be located in the center of the illustration as the avascular area are made obscure by the reflection of the light used for photography. The dense network of vasa is at the adventitial-medial junction with penetration deeply into the media. (×30.)

Fig. 5. L mphatic duct in pig heart filled w th microcy talline barium sulfat that was injected into the coronary artery sa orum l mphorum contain India ink injected int the coronary ein The absence of ink in the barium suggests that these asa do not comm nicat with the lumen of the underly g lymphatic channel. (×30.)

Fig. 6. Three tructures frequently seen in pig heart At the left of the photogr ph the whi ish ppearing are is coronary artery wall w th perficial and deep adventitial asa orum. To the right of the center is the typical interwoven pattern of sa ners orum thin ners tru k Bet n these t tructures and lightly broader than the ners l paracoronary lymph duct containing arterial injection ma hich ha fox lated lightly The ein is t the right of these tructures but is not included i the ill tration. (×25.)

Table I Correlation of clinical data with intramural hemorrhage

Case	*Age (yr)*	*Sex*	*LVH*	*MCI (old)*	*HBP*	*IMH*
1	[redacted]	M	+	—	+	+
2	55	M	0	—	+	+
3	54	M	—	—	+	+
4	56	M	—	—	+	+
5	52	M	+	—	+	+
6	56	M	+	—	+	+
7	65	M	—		+	+
8	25	M	—	—	+	+
9	49	M	+	—	+	+
10	74	M	0	—	+	+
11	59	M	0		+	+
12	75	M	—	—	+	+
13	60	M	—		+	+
14	59	F	—	—	+	—
15	60	F	+		+	+
16	74	F	+	—	+	+
17	70	F	+	—	+	+
18	78	F	—	+	+	+
19	71	F	+	+	+	+
20	72	F	+	+	+	—
21	66	M	—	—	—	—
22	83	M	—	+	—	+
23	60	M	—	—	—	—
24	[redacted]	M	—	—	—	+
25	3/12	M	0	—	—	—
26	50	M	—	—	—	—
27	44	M	—	—	—	+
28	51	F	—	—		—
29	87	F	—	—		—
30	10/12	F	—	—	—	—

+ present — absent 0, no information LVH, left ventricular hypertrophy MCI, myocardial infarction, HBP hypertension IMH intramural hemorrhage.

probably is greater than that observed The question of whether intramural hemorrhage correlates with the history of hypertension has been raised by Paterson and associates [23] and findings in this report suggest such a correlation particularly its occurrence in one 25-year-old hypertensive subject in our series. It is noteworthy that intramural hemorrhage was observed in eight of nine patients in whom left ventricular hypertrophy was described. It may be pertinent that hematologists have recognized a bleeding tendency in hypertensive persons related to a defect in the capillary wall.[22,23] From the clinical records in our series it was not possible to determine the severity or duration of hypertension in some patients, though most were chronically and moderately hypertensive

In areas about calcified atheromas and intramural hemorrhages the density of intramural capillaries was greater than in other areas The significance of these observations is uncertain whether extent of vascularization correlates with the severity of atherosclerosis, and whether vascularization is causally related to the lesions or follows them is not known. In young nonatherosclerotic pigs intramural blood vessels and hemorrhages were not seen

Adventitial and intramural vasa of coronary veins in pigs and humans were plentiful and veins were free of atherosclerosis. This raises the question of whether the extensive endowment of veins with vasa and or the relatively passive function and low pressure within veins are contributing factors in protecting them from atherosclerosis. Recent studies by Penn and associates in thyroidectomized dogs fed

high cholesterol diets indicated that venous homografts placed in the peripheral arterial system developed minimal atherosclerosis in contrast to severe lesions produced concomitantly in the arterial system. Though intravascular pressure and many metabolic factors contribute significantly to the pathogenesis of atherosclerosis in general, the disturbance of function of vasa of the venous grafts resulting from preparation for transplantation must be considered as a factor in the production of changes in the grafts. Possibly development of coronary arterial intramural vascularization in atherosclerosis is a mechanism for the preservation of arterial wall function, whereas intramural vasa of veins are present normally early in life and serve to maintain their normal wall function.

In young nonatherosclerotic pigs blood vessels and lymphatics communicate freely as evidenced by the presence in lymphatics of mass injected into arteries and/or veins. Also mass injected directly into lymphatic vessels appeared in venous channels. Communications between the blood vascular system and lymphatics may occur between veins and lymphatics as observed in peripheral lymphaticovenous communications,[2, 25] or at a capillary level near the apex of the heart which would help to explain the pattern of appearance of arterial injection mass in lymphatics. Another possibility is communication between arteries and veins whereby arterial injection mass enters the venous system and then lymphatics via lymphaticovenous communications. Anatomical communications between blood vessel and lymphatics were not identified but the particle size of the injectate and the rapidity with which it appeared in lymphatics in good concentration, as well as its absence in surrounding tissues, precluded its having reached the lymphatics via diffusion through intervening tissues. An incidental finding was the presence of blood capillaries (vasa vasorum lymphorum) about the wall of lymphatic channels. There was no evidence that these capillaries communicated with the lumen of lymphatics (Fig. 5). In humans with coronary atherosclerosis none of these phenomena was observed. Since our series does not include atherosclerotic pigs or adequate studies of young nonatherosclerotic human subjects, correlation between the presence or absence of lymphatics and the degree of atherosclerosis cannot be made. Vessels that could be identified as lymphatic[9] were not recognized intramurally or in areas of atheroma. It is interesting to speculate whether the presence of atherosclerosis may have interfered with the demonstration of lymphatics in humans or possibly the presence of abnormalities of lymphatic drainage may have contributed to the development of atherosclerosis.

Poor filling of vasa nervorum in man conceivably may be a reflection of impairment of blood supply to cardiac nerves by atherosclerosis. Ischemic nerves may have a detrimental effect on the neural control of coronary blood flow and regulation of heart rate.[27] Roberts[11,28] has suggested that impairment of blood supply to cardiac nerves may be a factor in the production of angina pectoris. The mechanism by which trinitroglycerin and allied drugs relieve angina pectoris could be due in part to increase of blood flow into vasa vasorum and vasa nervorum. In the current series, correlation with the clinical history of angina pectoris was not attempted.

The results of this study relating to anatomic variations of vasa vasorum between normal and atherosclerotic coronary vessels are inconclusive. Since adequate studies of normal humans and abnormal pigs have not been made, significant clinical correlations are not possible. If the course of atherosclerosis in pigs is similar to that in man, it can be speculated that nonatherosclerotic coronary arteries have no intramural vasa vasorum and that intramural vascularization is present as a result of atherosclerosis. The role of vasa vasorum in the pathogenesis of coronary atherosclerosis has yet to be explained.

Summary

The anatomy of vasa vasorum of coronary arteries, veins, and lymphatics, and of vasa of cardiac nerves in swine and man was described. Intramural vasculature and hemorrhages in coronary arteries were prominent in man in the presence of atherosclerosis and hypertension but were not observed in nonatherosclerotic pigs. Communications between the blood vascu

lar system and lymphatics occurred in hearts of young pigs but were not observed in the human hearts studied. The clinical correlations of the study were inconclusive but suggested possibilities for further investigation. Other similarities and differences of the cardiac microcirculation in the two species and their possible significance were discussed.

The authors express appreciation for the encouragement of Dr. J. C. Paterson and for the technical assistance of James R. Dumas and Dr. Wayne T. Lamar.

REFERENCES

1. Winternitz, M. C., Thomas, R. M., and Le Compte, P. M.: The biology of arteriosclerosis, Springfield, Ill., 1938, Charles C Thomas, Publisher.
2. Paterson, J. C.: Vascularization and hemorrhage of the intima of arteriosclerotic coronary arteries, Arch. Path. 22:313, 1936.
3. Paterson, J. C.: Capillary rupture with intimal hemorrhage as a causative factor in coronary thrombosis, Arch. Path. 25:474, 1938.
4. Wartman, W. B.: Occlusion of the coronary arteries by hemorrhage into their walls, Am. Heart J. 15:459, 1938.
5. Patek, P. R.: The morphology of the lymphatics of the mammalian heart, Am. J. Anat. 64:203, 1939.
6. Miller, A. J., Pick, R., and Katz, L. N.: Ventricular endomyocardial pathology produced by chronic lymphatic obstruction in the dog, Circulation Res. 8:941, 1960.
7. Miller, A. J., Pick, R., and Katz, L. N.: Lymphatics of the mitral valve of the dog, Circulation Res. 9:1005, 1961.
8. Miller, A. J.: Lymphatics of the heart, Arch. Int. Med. 112:501, 1963.
9. Johnson, R. A., and Blake, T. M.: Lymphatics of the heart, Circulation 33:137, 1966.
10. James, T. N.: Anatomy of the coronary arteries, New York, 1961, Hoeber Medical Division, Harper & Row, Publishers, Inc.
11. Roberts, J. C., Jr., and Straus, R.: Comparative atherosclerosis, New York, 1965, Harper & Row, Publishers, Inc.
12. Spector, W. S.: Handbook of biological data, Philadelphia, 1956, W. B. Saunders Company.
13. Sobin, S. S., Frasher, W. G., Jr., and Tremer, H. M.: Vasa vasorum of the pulmonary artery of the rabbit, Circulation Res. 11:257, 1962.
14. Williams, T. W., Jr.: The visualization of vertebrate capillary beds by intravascular precipitation of lead chromate, Anat. Rec. 100:115, 1948.
15. Stone, J. E., Frothingham, R. E., and Johnson, R. A.: Styrene as a clearing agent, Stain Tech. 39:183, 1964.
16. Sunderland, S.: Blood supply of nerves of the upper limb of man, Arch. Neurol. & Psychiat. 53:91, 1945.
17. Adams, W. E.: The blood supply of nerves. I. Historical review, J. Anat. 76:323, 1942.
18. Roberts, J. T.: The role of the small vessels and nerves of the heart in heart failure, coronary thrombosis, and cardiac pain, Med. Ann. District of Columbia 14:483, 1945.
19. Koch, F. C., and Hanke, M. E.: Practical methods in biochemistry, ed. 6, Baltimore, 1953, The Williams & Wilkins Company.
20. West, E. S., and Todd, W. R.: Textbook of biochemistry, ed. 3, New York, 1961, The Macmillan Company.
21. Paterson, J. C., Mills, J., and Lockwood, C. H.: The role of hypertension in progression of atherosclerosis, Canad. M. A. J. 82:65, 1960.
22. Griffith, J. Q., and Lindauer, M. A.: Increased capillary fragility in hypertension: incidence, complications, and treatment, Am. Heart J. 28:758, 1944.
23. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the blood, ed. 8, New York, 1957, Grune & Stratton, Inc.
24. Penn, I., Schenk, E., Rob, C., Deweese, J., and Schwartz, S. I.: Evaluation of the development of atherosclerosis in autogenous venous grafts inserted in the peripheral arterial system, Circulation (Suppl. 1) 32:192, 1965.
25. Threefoot, S. A., Kent, W. T., and Hatchett, B. F.: Lymphaticovenous and lymphaticolymphatic communications demonstrated by plastic corrosion models of rats and by postmortem lymphangiography in man, J. Lab. & Clin. Med. 61:9, 1963.
26. Threefoot, S. A., and Kossover, M. F.: Lymphaticovenous communications in man, Arch. Int. Med. 117:213, 1966.
27. Berne, R. M., Degeest, H., and Levy, M. N.: Influence of the cardiac nerves on coronary resistance, Am. J. Physiol. 208:763, 1965.
28. Roberts, J. T.: The effect of vascular occlusive diseases of the extremities on the blood supply of nerves. Experimental and clinical studies on the role of the vasa nervorum, Am. Heart J. 35:369, 1948.

Case reports

"Wedensky facilitation" in the human heart

Report of a probable case

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Recent reports of studies using electrical pacemakers as a method of treatment of advanced heart block suggest that certain electrophysiologic properties of neuromuscular tissue described 80 years ago by Wedensky may be applicable to human cardiac electrophysiology.[1] The Wedensky effect, described in 1887[2] in a neuromuscular preparation of the frog and defined as the ability of a subthreshold stimulus to become threshold and to evoke a response if preceded by a "strong" stimulus, was demonstrated in the Purkinje fiber of the dog heart by Goldenberg and Rothberger in 1933 and has been championed by Scherf and Schott as a significant mechanism of arrhythmias. This phenomenon was demonstrated for the human heart by Castellanos and associates in 1966.

In 1903 Wedensky[4] observed that an impulse arriving at an area of complete block lowers the threshold of excitation of the nerve below the area of the block. Hodgkin[7] showed that the increased excitability beyond the block is due to an extrinsic potential produced by an electrotonic current. This phenomenon is known as Wedensky facilitation. It is the purpose of this report to present an instance of malfunctioning cardiac pacemaker in which the pacemaker stimulus elicited a response (1) when falling during the supernormal period of ventricular recovery or (2) when synchronous with or closely following the P wave. It is suggested that Wedensky facilitation might possibly explain the response to the stimuli which are related to the P waves.

Case report

The patient, a 47-year-old woman, was admitted to the Indiana University Medical Center on August [illegible], 1961, for the management of complete heart block of obscure etiology with almost continuous Adams-Stokes episodes. The mechanism of the Adams-Stokes attacks was ventricular tachycardia terminating in fibrillation which did not respond to drug therapy and had to be controlled with repeated electrical shock over the next 12 hours and finally by stimulation through a transjugular pacemaker until a pacemaker could be surgically implanted. The patient remained asymptomatic until November 17, 1963, when she was readmitted because of malfunctioning of the pacemaker. An electrocardiogram (ECG) taken on admission (Fig. 1) showed sinus rhythm with a 2:1 atrioventricular (AV) block. The pacemaker stimuli elicited a response only

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The ECG of [illegible] case was demonstrated for the authors by Dr. K. Greenspan [illegible] the discussion of paper by F. R. Artel and co-workers at the Second Conference on Paired Pulse Stimulation and Postextrasystolic Potentiation in the Heart held in New York on May 12 and 13, 1967.

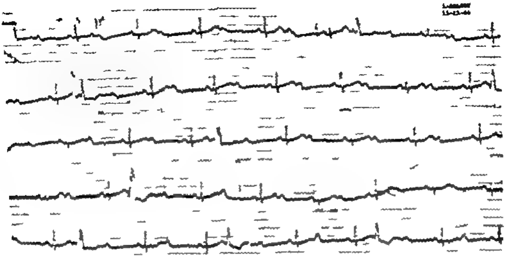

Fig. 1 The dominant rhythm is sinus in origin with a rate of 75 and a 2:1 AV block. The artificial pacemaker discharges at a rate of 65 per minute. Ventricular responses are elicited by the artificial pacemaker whenever the latter falls in the supernormal phase.

Fig. 2 The dominant rhythm is sinus in origin with rate of approximately 75 and 2:1 AV block. The artificial pacemaker elicits entricular response when it falls on top of P or in the supernormal phase. The diagram inserted in the bottom row is composite of these impulses.

when falling within a R-to-stimulus interval varying from 0.44 to 0.60 second, the supernormal period of excitability.

An ECG (Fig. 2) recorded on November 24 1964 again revealed a 2:1 AV block with ventriculophasic sinus arrhythmia with the shorter P-P interval varying from 0.70 to 0.80 and the longer P-P from 0.80 to 0.84. ith the pacemaker stimulus eliciting a esponse during the supernormal period. I addition however entricular excitation was recorded when the stimulus fell on top of or shortly after P. Four such stimuli ar re corded one each in rows 1 2 4, and 6, with the third entricular complex in row 4 being a fusion (combination) beat resulting from the normally transmitted impulse fusing with excitation resulting from the pacemaker stimulus. The response to the stimulus in row 5 is not accompanied by a clearly

defined P wave. If one were to assume a P-P interval of 80 (the long interval of the ventriculophasic sinus arrhythmia) from the immediately preceding P wave, one has to conclude that the response to the stimulus of that particular complex is not related to the P wave.

Stimuli falling on P waves with an R-to-stimulus artifact of 80 to 81 do not result in ventricular activation (e.g., stimulus artifact 10, 9, 3, and 9 in rows 1, 3, 4, and 5, respectively) probably because of falling in the refractory period of the preceding QRS.

Comment

Excitation of the ventricle by a subthreshold stimulus synchronous with atrial depolarization can be explained by Wedensky facilitation. The atrial potential resulted in lowering of the strength of the stimulus required to elicit a ventricular response. Since the response of the human heart to a stimulus depends on both the threshold of stimulation and conduction, it is impossible to state whether the effect observed in this case was one of lowered threshold for stimulation or intraventricular conduction.

This case is not presented as an unequivocal example of Wedensky facilitation but as an unusual tracing which can in part be explained by invoking the phenomenon of facilitation. Our observation needs to be confirmed by additional clinical cases, and the proposed mechanism investigated and proven, if possible, in the experimental animal.

Summary

A probable example of Wedensky facilitation in the human heart is reported.

REFERENCES

1. Fisch, C., and Greenspan, K.: Wedensky observations, Circulation 35:819, 1967.
2. Wedensky, N. E.: Über die Beziehung zwischen Reizung und Erregung in Tetanus, Berlin Acad. Wiss. 51:96, 1887.
3. Goldenberg, M., and Rothberger, C. J.: Untersuchungen an den specifischen Muskulatum des Hundeherzens, Ztschr. ges. Exper. Med. 90:508, 1933.
4. Scherf, D., and Schott, A.: Extrasystoles and allied arrhythmias, London, 1953, William Heinemann, Ltd., p. 500.
5. Castellanos, A., Jr., Lemberg, L., Johnson, D., and Berkovits, B. V.: Wedensky effect in the human heart, Brit. Heart J. 28:276, 1966.
6. Wedensky, N. E.: Die Erregung, Hemmung und Narcose, Pflugers Arch. ges. Physiol. 100:1, 1903.
7. Hodgkin, A. L.: Evidence for electrical transmission in nerve, J. Physiol. 90:183, 1937.
8. Arbel, E. R., Langendorf, R., Pick, A., and Katz, L. N.: The effect of atrial depolarization on the response to subthreshold stimulation of the ventricles. A preliminary report of clinical and experimental observations, to be published.

A case of idiopathic myocardiopathy with deposits of a peculiar substance in the myocardium; diagnosis by endomyocardial biopsy

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In recent years, much attention has been paid to certain cases of cardiac enlargement of unknown etiology. Since the specific etiologies have not been defined, different terminologies have been applied, such as primary myocardial disease,[1-5] myocardosis,[6] idiopathic cardiac hypertrophy, and idiopathic cardiomyopathy. It is now believed that the diagnosis of primary myocardial disease or idiopathic myocardiopathy should be based on positive evidence rather than a mere exclusion of all known etiologies. In this respect, it is evident that biopsy of the heart can provide positive if not definitive evidence for diagnosis.

The purpose of the present report is to present the case of a 22 year-old man with idiopathic myocardiopathy in whom light and electron microscopic as well as histochemical studies were performed on an endomyocardial biopsy specimen obtained with the Konno intravascular biopsy catheter or bioptome. It should be emphasized that pathophysiological studies of the disease are possible by correlating biopsy findings with almost simultaneously obtained hemodynamic values. Autopsy specimens represent only the morphological changes in the final stage in a series of pathologic processes, which may also be altered seriously during the agonal and postmortem autolytic periods.

Case report

Y. M., a 22 year-old Japanese man, had been found on routine examination, to have a slightly enlarged heart five years prior to admission. He had been entirely asymptomatic and was hospitalized for cardiac evaluation on July 20, 1965. He had had diphtheria at the age of two and high fever of unknown etiology at 11 years of age. No family history of cardiovascular disease could be obtained. After discharge from the hospital in October, 1965, the patient was well until February, 1966, when he noticed occasional irregular beats followed by the onset of Stokes-Adams attacks due to complete A-V block towards the end of March. He was again hospitalized on an emergency basis and isoproterenol was given. As the attacks recurred despite drug therapy, an electric pacemaker (TR 14, Electrodyne Co.) was implanted on April 29, 1966. The postoperative course was uneventful except for

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The case was partly presented at the symposium on "Idiopathic myocardial fibrosis and allied diseases" in the 30th Annual Meeting of the Japanese Circulation Society on March 29, 1966 in Kyoto.
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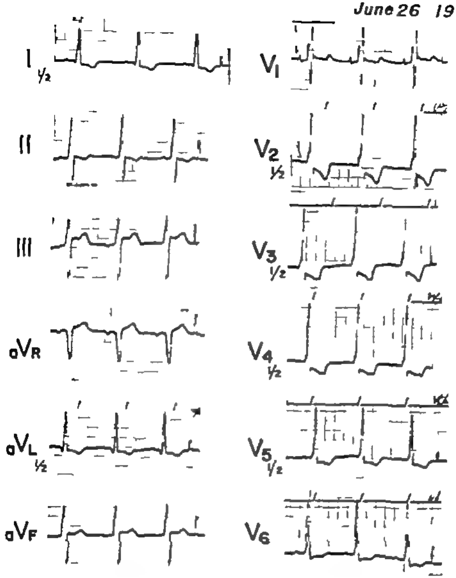

Fig. 1. Twel lead ECG obta ned on admission. First-degree A V block, right bundle branch block, and left ventricular hypertrophy

transient competition between the artificial electric and the sinoatrial pacemaker which subsided under reserpine therapy. The patient wa discharged three month after impla tation.

Physical examination on the first admission in July 1965 rev aled well-developed, w ll-nou ished, healthy looking young man with regular pulse of 8 beat per m nute blood pressure of 128/63 mm Hg, nd a normal temperature. His face was fl shed but no telangiectases were noted. Th neck ein were not distended. The lu gs were cle to percu ion nd scultat on. There was bulging of the left ide of the anterior chest wall. The heart enlarged nd a left ent icular hea was felt t the left terior axillary l ne. A high pitched Grade 3/6 m l y tolic murmur was best heard at the second left ternal border. The second sound at the second left ternal border was widely split but varied a little with respiration i the normal fashion. The splitting of the second sound became almost fixed later hen the patient de eloped syncopal episodes. There wa a fourth sound at the pex. The liver and the pleen ere not palpable. The remainder of the physical examination was normal.

Laboratory tudies revealed a hemoglobin of 93 per cent (Sahli) a hematocrit of 43.5 per cent red blood ll cou t of 415 by 10^4 per cubic milli meter and whit blood cell ou t of 7,300 with a normal differential. The urinalysis w normal. The C-reactiv protein and the heumatoid arthritis (RA) test w re negativ. The antistreptolysin-O t ter (ASLO) w positiv in dilution of 1 166, and the blood sedimentation rat wa 1 mm in one

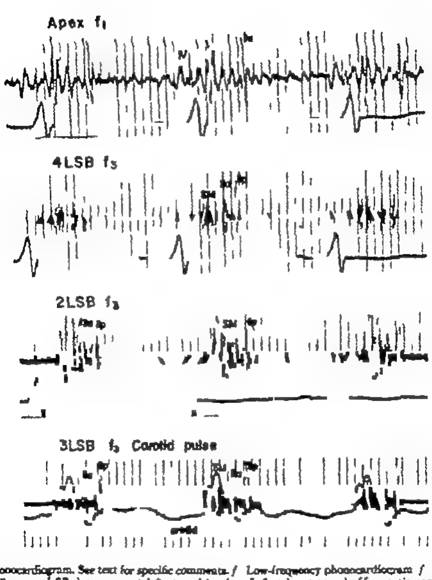

Fig. 2. Phonocardiogram. See text for specific comments. *f* Low-frequency phonocardiogram *f* mid-frequency phonocardiogram *LSB* Interspace at left sternal border *I* first heart sound *II* aortic component of the second sound *IIp* pulmonic component of the second sound *IV* fourth heart sound *SM* systolic murmur *Carotid* external carotid pulse

hour (Westergren). Serum proteins were 5.8 Gm. per 100 ml., with 48.6 per cent albumin, 3.8 per cent α_1- 7.5 per cent α_2- 21.1 per cent β- and 19.0 per cent γ-globulins. The albumin/globulin (A/G) ratio was 0.9. The serum cholesterol was 130 mg. per 100 ml., with an ester fraction of 68.3 per cent. The basal metabolic rate was 25 per cent, and the ¹³¹I uptake normal. Serum glutamic oxalacetic transaminase (SGOT) was 27 units, serum glutamic pyruvic transaminase (SGPT) 16 units, and lactic dehydrogenase (LDH) 450 units. The complement fixation reactions for various viruses were positive in a titer of 1:4 for polio I, negative for polio II and III, positive in a titer of 1:8 for Coxsackie B, 1:4 for herpes, and negative for mumps and J panese encephalitis. Liver and kidney functions were normal. An electrocardiogram (ECG) (Fig. 3) showed first-degree A-V block, right bundle branch block, and left ventricular hypertrophy. A phonocardiogram (Fig. 2) revealed a diamond-shaped systolic ejection murmur best recorded at the second left sternal border. A fourth sound was present at the apex. It was interesting to note that the splitting of the second sound was due to early appearance of the aortic component of the second sound in relation to electrical systole. The interval between the Q wave in the ECG and the beginning of the aortic component of the second sound (IIa) in the phonocardiogram was 0.33 second, while the QT interval in the ECG measured 0.45 second. These values indicate a short mechanical systole (QII) and a long electrical systole (QT) at the heart rate of 62 beats per minute (Hegglin's syndrome (energetisch-dynamische Herzinsuffizienz).

Fig 3A Chest roentgenogram posteroanterior iew t ken March 1960 the rdiac silhouett hows the pper l m ts of normal in size

Fig 3B Chest roentgenogram pc teroa terior iew taken on Dec 4 1965 how g defi it rdiomegaly especially in left lower segment

Table I Physiological data

	Pressures (mm Hg)	O content (vol per cent)
Superior ena cava (m)	5	13 2
I ferior ena ca a (m)	6	12 5
Right atri m (m)	5	14 4
Right vent icl		
inflow		
	37	13 7
d	4	
e-d	[illegible]	
outflow		
	36	13 2
d	2	
e-d	6	
Left pulmonary artery		
	30	13 4
d	13	
m	18	
Left ventricle		
	136	
d	5	
e-d	13	
Ascending aorta		
	122	19 3
d	66	
m	85	
A V O₂ difference (ol per cent)	5 90	
Cardiac ndex (L./min./M)		
Fick method	2 56	
Dye method	2 49	

*s, Systolic pressure e-d end-diastolic pressure d diastolic pressure m, mean pressure

A chest roentgenogram (Figs. 3 1 and 3B) howed progress cardiomegaly especially in the left lower segment sinc March 1960. Right nd left heart catheteriz tion (Table 1) revealed slightly ele ted end-diastolic pressures with prominent wa es in the right nd left entricles (Fig 4). The cardiac index was low by both the Fick and the dy method There was no significant pressure gradient across ny of the four heart lves or in the outflow tract of either entricle Significant sh t t any level ere ruled out on the basis of blood oxygen studies.

Endomyoc rdial biops After routine right heart catheterization Konno biopsy catheter or "biop-tome w introduced i t the right entricle in the left antecul tal m (Fig 5) A small specimen of ardiac tissue 3 1 y 2 mm including endocardium nd m ocard um, excised from the pical region of the right entricle Needle biopsy of the left en tricula terior ll f om the epicardial surfac w perf ormed ten months later during thoracotomy for implantation of an lectric pacem ker

H stological find g of the biop y specimen

RIGHT E T ICLE There w no signific t fi brosis cellular i filt tion stor e of bnormal subst nce i the interst tial tissue or marked hyper

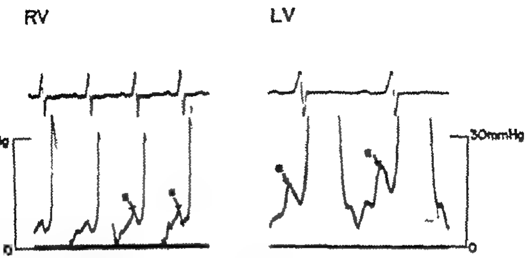

Fig. 4. Right and left ventricular pressure tracings showing elevated end-diastolic pressure and prominent waves.

Fig. 5. Chest roentgenogram showing Konno biopsy catheter or "bioptome" introduced into the right ventricle via the left antecubital vein.

trophy of muscle fibers. In almost all muscle fibers, however, diffusely stained or granular substance of peculiar nature was stored in the widened sarcoplasmic space; occasionally it occupied the whole section of a muscle fiber with apparent loss of myofibrils (Fig. 6). The substance was stained light red with eosin, blue with aniline blue, and light khaki with van Gieson elastic stain. Histochemically it was frequently weakly periodic acid-Schiff (PAS)-positive and disappeared following digestion with saliva. The colloidal iron reaction and Alcian blue staining for acid mucopolysaccharide, pyronin-methyl green staining for ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), Congo red staining for amyloid, the ferric ferricyanide method of Chèvremont and Frédéric for sulfhydryl (SH) groups, and Prussian blue method for iron were all negative.

LEFT VENTRICLE. The peculiar substance deposited in the muscle fibers of the right ventricle was also found in the left ventricle. Staining and histochemical properties of the substance were identical with those described above. A severe degree of interstitial fibrosis in the left ventricular myocardium, however, was the prominent feature different from the right (Fig. 7). The heart muscle fibers were surrounded and partly replaced by dense collagenous tissue.

Electron microscopic findings of the biopsy specimen. The biopsy specimen was cut into 0.5 × 1.0 mm cubes, fixed in phosphate-buffered osmium tetroxide, dehydrated through a graded series of alcohols and propylene oxide, and embedded in Epon. Sections were made with a Leitz Ultratome, stained with uranyl acetate, and examined with Hitachi HS-11A electron microscope. In many sarcoplasmic spaces there were peculiar fine fibrous structures running in various directions (Fig. 8). At higher magnification the fibrous structures revealed a tubular appearance measuring approximately 50 to 80 Å in diameter and were tightly tangled together in the sarcoplasm. There was no period of the structure. Besides the fibrous structures, previously undescribed pigment granules consisting of a number of spherical osmiophilic material of varying size were found in the sarcoplasm (Figs. 9 and 10). Some of the granules with less opaque structureless portion at the periphery

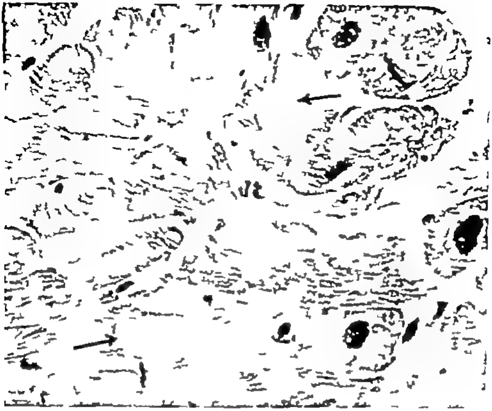

Fig 6 Right entricular myocardium of biopsy specimen obtained by the Konno biopsy catheter or "bioptome Not diffusely stained or granula substance (arrows) in the widened sarcoplasmic space (Hematoxylin nd eosi × 320)

Fig 7 *Left* entricular *myocardium of needle biopsy specimen* o*btained d ring thoracot my for* impla tation of an electric pacemaker Arrow show the imilar dep its seen i the muscle fibers of the right entricle There is severe degree of interstitial fibrosi the heart mu le fiber re surrounded nd partly replaced by dense collagenous tissue (Hematoxyli nd eosin × 320)

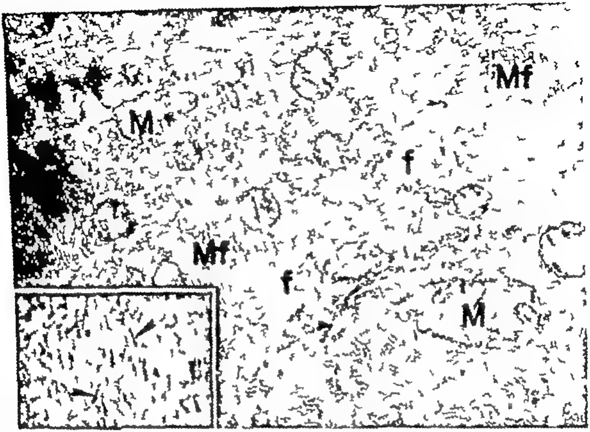

Fig. 8. Electron micrograph of left ventricular myocardium. Note peculiar fine fibrous structures (*f*), scarce myofibrils (*Mf*) and definitely abnormal mitochondria (*M*). (× 20,000.) The peculiar fibrous structures at the higher magnification are shown at the left lower corner with arrows. (× 100,000.)

were distinctly limited by the membranous structure in the sarcoplasm while the others were not enclosed by definite membranes (Figs. 9 and 10). The myofibrils and mitochondria were very scarce in almost all sections (Figs. 8, 9 and 10). Most of the mitochondria were definitely abnormal: some were small whereas others were swollen and had few or no cristae (Figs. 8, 9 and 10). Besides the abnormal mitochondria and pigment granules, there were numerous vesicular formations in the areas of the sarcoplasm where no myofibrils were seen (Fig. 9). They resembled the vesicles described in previous reports.[4, 5] No rough-surfaced sarcoplasmic reticulum was seen in this study. Glycogen granules seemed to be increased in number (Fig. 11).

Discussion

The most rewarding aspect of the present report is that a definite diagnosis could be made on the basis of a correlation of the physical and hemodynamic findings with the histopathology in a living patient. The histological studies were performed on a biopsy specimen obtained from the inner surface of the right ventricle by Konno's bioptome. The histological findings in the right ventricle were confirmed by similar changes in a specimen of left ventricular muscle obtained later during implantation of an electric pacemaker. Although the patient developed Stokes-Adams syndrome after discharge from the first admission and an electric pacemaker was implanted, there has been no evidence of congestive heart failure, either right or left. He continues to live a normal life without any difficulty even at present, when the third hospitalization is necessary because of the battery failure of the pulse generator.

The etiology of the disease in this case remains undetermined. Diphtheria at the age of two and a high fever of unknown cause at the age of 11 are probably not relevant, because a chest roentgenogram revealed the heart size to be still in the upper limits of normal or only slightly

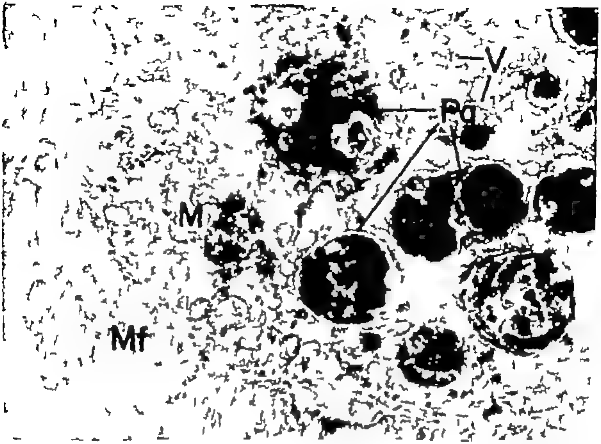

Fig 9 Pigment granules (*Pg*) consisting of a number of spherical osmiophilic materials of varying size in the left ventricular myocardium Abnormal mitochondria (*M*) and vesicular structures (*V*) are seen. Peculiar fibrous structures (*f*) are also present in the sarcoplasm where myofibrils (*Mf*) are very scarce (× 12,500.)

enlarged five years prior to admission Fairly recent viral infections were ruled out on the basis of complement fixation titers for various viruses. Progressive cardiomegaly of five years duration however still suggests the possibility that some type of infection in the past may have been responsible for the disease and the histological changes in the myocardium may represent residuals of repair of old infections Alcoholic cardiomyopathy [4] was ruled out since the patient is not an alcoholic. Nutritional deficiency with or without alcoholism [12] and metabolic disorders of the myocardium described in previous reports [1] are only remote possibilities because the dietary pattern thyroid function and serum electrolytes are normal although there are some abnormalities in serum proteins i e decreased total protein albumin and the A/G ratio and increased α-globulin

The presence of right bundle branch block during sinus rhythm (Fig 1) is of interest in view of the fact that the patient later developed recurrent Stokes-Adams attacks due to complete A V block Fortal and associates [3] reported a high incidence of right bundle branch block during sinus rhythm in patients who required an artificial pacemaker to prevent recurrent Stokes-Adams attacks when heart block developed The authors have reported similar cases, including this patient elsewhere

The hemodynamic and phonocardiographic studies ruled out the possibility of operable congenital heart diseases including anomalous left coronary artery arising from the pulmonary artery and idiopathic hypertrophic subaortic stenosis (IHSS) Prominent "a" waves in the right and left ventricular pressure tracing or "atrial kick" [12] elevated end-diastolic pres-

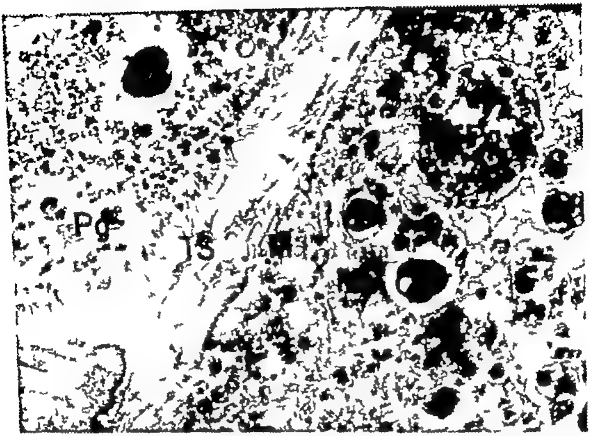

Fig. 20. In the left ventricular myocardium some of the pigment granules (*Pg*) are limited by the membranous structure while the others are not. Some of the constituents of the pigment granules are dispersed into the sarcoplasm. The myofibrils (*Mf*) are extremely scarce. *M*, Mitochondria; *IS*, interstitial space. (× 12,500.)

sures of both ventricles, and the presence of a prominent fourth sound suggest the reduced compliance of both ventricles. These hemodynamic findings, together with normal atrial mean pressures and the absence of pressure gradients across any of the four heart valves or in the outflow tracts of both ventricles, are compatible with those seen in patients with idiopathic myocardial hypertrophy without congestive heart failure or obstruction to blood flow. At the same time, the present case demonstrates distinct differences, clinically and hemodynamically, from patients with primary myocardial disease who develop recurrent episodes of congestive heart failure as often reported.[29] Thus, reduction of right and left ventricular compliance in this patient suggests fibrosis, thickening, or reduction in number of myocardial fibers which will be confirmed later by the light and electron microscopic studies of the biopsy specimen from the ventricles.

Among various methods[32,33] of biopsy of the human heart as an aid to diagnosis in endocardial and myocardial disease, the biopsy catheter or bioptome introduced by Konno and Sakakibara has been proved practicable and safe.[34] We have performed the endomyocardial biopsies of the right and left ventricles with Konno's intravascular biopsy catheter in more than 70 patients without serious complications.

Although preservation of the morphologic integrity of the myocardium for long periods of time after death has been possible in the rat,[35] histological studies of the autopsy specimen always raise the possibility that agonal as well as postmortem changes may have contributed to the genesis of some of the abnormalities. The problem is especially serious in elec-

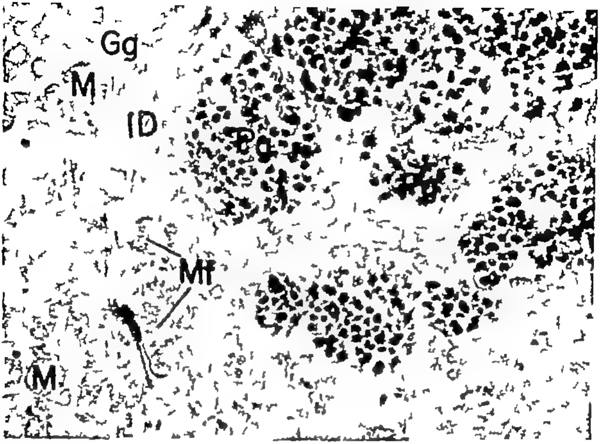

Fig. 11. Glycogen granules (*Gg*) in the left ventricular myocardium seem to be increased in number. Pigment granules (*Pg*), myofibrils (*Mf*), mitochondria (*M*) of varying size and intercalated disc (*ID*) are indicated. (× 12,500.)

tron microscopic studies. Moreover, autopsy specimens represent nothing but the final stage of the disease, which is certainly different from the stage when clinical studies are performed. Therefore, there is no doubt that heart biopsy is the only method of providing useful morphological and histochemical information in studying the pathophysiology of this disease.

The morphological features of the peculiar deposits in the myocardial fibers in this case resemble those of the deposits of a fibrillar polysaccharide reported by Ferrans and associates[28] and of the peculiar substance in the sarcoplasmic space in Case 3 of Kawamura and Hayashi.[7] Histochemical studies, however, demonstrate that the peculiar deposits in the present case are not acid mucopolysaccharide, RNA, DNA, amyloid, SH compound, or iron. The deposits are very similar to those seen in Case 3 of Kawamura and Hayashi, but the sporadic deposition of a basophilic substance which they described cannot be seen. The weakly PAS-positive reaction of the deposits may be due to glycogen, probably not to the fibrous material itself. A strongly PAS-positive reaction, however, was never obtained in the substance. It seems apparent, therefore, that the deposits in this case also differ histochemically and morphologically from basophilic or mucoid degeneration[27,30] or Type I and Type II cardiac colloid,[72] although the limited histochemical studies in this report provide no adequate justification for definite conclusions. Thus the nature of the deposits seen in the present study still remains undetermined.

The ultrastructural features of the peculiar fine fibrous structures, which probably represent the peculiar deposits in the myocardial fibers on light microscopy, are very similar to those reported previously.[7]

However, pigment granules in the sarcoplasm consisting of spherical osmiophilic materials, which may also represent the granular part of the peculiar deposits on light microscopy, have not been reported in any previous study. The myelin-like and other dense granules previously reported have some similarity in location and gross appearance, but the detailed morphology seems different; the granules in our case are more circular and regular in over-all shape when limited by the membrane, and the small spherical osmiophilic constituents of the granules are more distinct from each other, with less tendency to agglomeration (Figs. 10 and 11). In fact, some of them are dispersed into the sarcoplasmic spaces (Fig. 10). Although the nature and significance are not obvious at present, it seems reasonable to assume that the presence of the peculiar fibrous structures and pigment granules represent some degradation process in the muscle cells. It could be stated that the ultrastructural aspects in this case, including the accumulation of the peculiar fibrous structures, pigment granules, numerous vesicular formations, and scarcity of myofibrils or abnormal mitochondria, represent the presence of abnormal metabolic processes and severe interference with the normal function of the myocardial cells.

Summary

A case of idiopathic myocardiopathy in a 22-year-old man has been described. The diagnosis was made on the basis of physical, extensive graphic, and hemodynamic studies and confirmed by endomyocardial biopsy with Konno's intravascular biopsy catheter or bioptome.[6]

The necessity for biopsy specimens for histochemical and electron microscopic studies and the superiority of Konno's bioptome have been discussed briefly.

Light and electron microscopic studies on the biopsy specimen from the heart revealed the accumulation of peculiar fine fibrous structures and pigment granules in the sarcoplasm, which suggest some degradation process resulting from abnormal metabolism and functions in the myocardial cells. The histochemical properties of the peculiar substances have also been described.

The reduced compliance of both ventricles was probably due mainly to the loss of myofibrils and increased interstitial fibrosis, which was confirmed by histological studies on the biopsy specimen and which presumably contributed to some of the peculiar physical and hemodynamic features in this case.

The patient developed recurrent Stokes-Adams attacks due to A-V block. He is now living a normal life with an implanted pacemaker. Although the etiology could not be determined in this case, the possibility of some type of infection, including virus infection, could not be completely ruled out.

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REFERENCES

1. Mattingly, T. W.: The clinical concept of primary myocardial disease. A classification and a few notes on management and prognosis, Circulation 32:845, 1965.
2. Fowler, N. O.: Classification and differential diagnosis of the myocardiopathies, Prog. Cardiovas. Dis. 7:1, 1964.
3. Blankenhorn, M. A., and Gall, E. A.: Myocarditis and myocardosis, Circulation 13:217, 1956.
4. Levy, R. L., and Von Glahn, W. C.: Cardiac hypertrophy of unknown cause, Am. Heart J. 28:714, 1944.
5. Goodwin, J. F., Gordon, H., Hollman, A., and Bishop, M. B.: Clinical aspects of cardiomyopathy, Brit. M. J. 1:69, 1961.
6. Konno, S., and Sakakibara, S.: Endo-myocardial biopsy, Dis. Chest 44:345, 1963.
7. Kawamura, K., and Hayashi, K.: Ultrastructural aspects of myocardial disease of unknown etiology, Jap. Circulation J. 30:1375, 1966.
8. Hibbs, R. G., Ferrans, V. J., Black, W. C., Weilbaecher, D. C., Walsh, J. J., and Burch, G. E.: Alcoholic cardiomyopathy. An electron microscopic study, Am. Heart J. 69:766, 1965.
9. Brigden, W.: Uncommon myocardial diseases. The non-coronary cardiomyopathies, Lancet 2:1179, 1957.
10. Burch, G. E., and Walsh, J. J.: Cardiac insufficiency in chronic alcoholism, Am. J. Cardiol. 6:864, 1960.
11. Evans, W.: Alcoholic cardiomyopathy, Am. Heart J. 61:556, 1961.
12. Alexander, C. S.: Idiopathic heart disease. I. Analysis of 100 cases, with special reference to chronic alcoholism, Am. J. Med. 41:213, 1966.
13. Portal, R. W., Davies, J. G., Leatham, A., and Siddons, A. H. M.: Artificial pacing for heart block, Lancet 2:1369, 1962.

14 Kawai, C Mita, Yamashita, K., Inoue K., Kashu, C and Takatsu, T The use of isoproterenol hydrochloride with special reference to the treatment of Stokes-Adams syndrome (in Japanese) J Jap Soc Int Med. 56:176 1967 (Abstract)
15 Braunwald E Lambrew C T Rockoff S D Ross, J J and Morrow A G Idiopathic hypertrophic subaortic stenosis I A description of the disease based upon an analysis of 64 patients, Circulation (Suppl 4) 30:3 1964
16 Braunwald E and Aygen M Idiopathic myocardial hypertrophy without congestive heart failure or obstruction to blood flow Clinical hemodynamic and angiocardiographic studies in 14 patients, Am J Med [illegible] 7 1963
17 Massumi, R A Rios, J C Gooch, A L Nutter D DeVita, V T and Datlow D W Primary myocardial disease Report of 50 cases and review of the subject Circulation 31:19 1965
18. Segal, J P Harvey W P and Gurel, T Diagnosis and treatment of primary myocardial disease Circulation 32:837 1965
19 Dye C L Rosenbaum D Lowe J C Behnke, R H and Genovese, P D Primary myocardial disease Part I Clinical features, Ann Int Med 58:426, 1963
20. Dye, C L Genovese, P D Daly W J and Behnke R H Primary myocardial disease Part II Hemodynamic alterations, Ann. Int. Med 58:442 1963
21 Berca B and Hemz, J Percutaneous myocardial biopsy J Lab & Clin. Med. 62:859 1963.
22 Sutton, D C., and Sutton, G C. Needle biopsy of the human ventricular myocardium Review of 54 consecutive cases Am. Heart J 60:364 1960
23 Bulloch, R. T Murphy M L. and Pearce M [illegible] Intracardiac needle biopsy of the ventricular septum Am J Cardiol. 16:227 1965
24 Weinemark J R., Sommer H M and Zlotnik, R S Endomyocardial biopsy Experimental study with catheter technique Am Heart J 2:675, 1966.
25 Hibbs R G and Black, W C Electron microscopy of postmortem changes in the rat myocardium, Anat. Rec. 14 :261 1963
26 Ferrans, V J Hibbs, R G Walsh, J J and Burch, G. E Cardiomyopathy cirrhosis of the liver and deposit of fibrilla polysaccharide Report of a case with histochemical and electron microscopic studies, Am. J Cardiol. I :457 1966
27 Brewer D [illegible] M yxoedema An autopsy report with histochemical observations on the nature of the mucoid infiltrations, J Path. & Bact 63:503 1951
28 Scotti, T M Basophilic (mucinous) degeneration of the myocardium Am J Clin. Path. 25:994 1955.
29 Haust M D Rowlands, D T J Garancis, J C and Landing B H Histochemical studies on cardiac colloid. Am. J Path. 40:185 1962

Review

Microcirculatory aspects of atherogenesis, thrombogenesis, and antiatherosclerotics

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There has been much disagreement about the capacity of the arterial wall to synthetize cholesterol. In fact, most workers[3] have concluded that endogenous sterol synthesis accounts for only a minor fraction of the cholesterol in atheromatous lesions. The results[4] obtained by modern techniques with radioactive acetic acid or cholesterol tend to confirm such a concept.

The majority of workers believe that cholesterol enters the arterial wall by filtration. Alterations in the permeability of the endothelium, basement membrane, and ground substance have been variously cited as the fundamental cause of the leakiness.

Review

Recent findings on morphological aspects of the arterial wall. In analyzing such leakiness, most studies concentrated on the transportation of cholesterol through the endothelial lining of the arterial lumen, and needless to say they are important. However, a new x-ray microscopy technique reported by Clarke[7] demonstrates that the media, including the innermost layers which traditionally had been believed to be avascular, have a rich distribution of vasa vasorum. Contrary to the traditional concept, the capillaries of vasa vasorum have been clearly revealed in the innermost layers of media and arteriovenous anastomosis has been found directly beneath the internal elastic lamina in the human aorta. The author[9,10] found the same pattern of distribution of vasa vasorum in aortas and the trunks of coronary arteries of dogs and rabbits.

These findings suggest the importance of leakage from vasa vasorum in the transportation of cholesterol into the arterial wall. Especially in tissues such as that of the artery with smooth muscle fibers constituting the arterial wall surrounding the vessel lumen, the fluids leaking from vasa vasorum into the media may tend to be pushed toward inner layers including subendothelial layers in the constriction phase of arterial pulsation.

Beja and Tavares[11] found that the destruction of vasa vasorum prevents atherosclerosis even under continuous hyperlipemia in rabbits. Their data might suggest also the importance of the leakage from vasa vasorum, not the endothelial lining of arterial lumen, as a main route for the infiltration of cholesterol into the arterial wall.

The electron microscopic observation of vasa vasorum of man, monkeys, dogs, and rabbits (Figs. 1 to 5). In studies of vasa vasorum special interest has been directed to the capillary and venule because the transportation of serous substance takes place mainly in these segments, composed of endothelial cells and basement mem-

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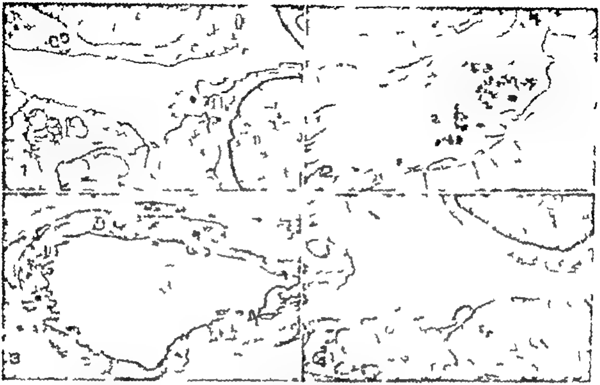

Figs. *1* to *4*. Capillaries with pores and thin protoplasm (B-type capillary) (*1*, in man; *2*, in rabbit) and capillaries with thick protoplasm without pores (A-type capillary) (*3*, in dog and *4*, in monkey). Arrows show the pore of endothelial cell. (Magnifications: Figs. *1*, *3*, and *4* ×18,000; Fig. *2* ×27,000.)

brane. In rabbits, which are markedly susceptible to atherosclerosis, approximately one fifth of the endothelial cells have an extremely thin protoplasm with so-called pores representing type B capillaries of Bennett and associates,[12] or visceral type capillaries of Fawcett,[13] and the remaining endothelial cells are type A capillaries of Bennett, i.e., muscle type capillaries of Fawcett. This was rather a surprising finding. On the other hand, the endothelial cells in the capillaries and venules of monkeys (*Macaca irus* and *Macaca fuscata*) and dogs, which are relatively resistant to atherosclerosis, show generally a rather thick protoplasm and pores could not be seen; these are typical type A[12] or muscle type[13] capillaries. In vasa vasorum of man there are many type A capillaries. However, it should be noted that Type B, i.e., visceral type capillaries are often found among these endothelial cells of man and their protoplasm is quite thin and the pores are found as in the case of visceral type capillaries of vasa vasorum of rabbits. Such pores of endothelial cells of vasa vasorum seem to be an important pathway for serous substances including cholesterol in man and rabbit. This structural similarity might also reflect on the enzymatic pattern of arterial wall. Actually, the similarity between man and rabbit in the composition of lecithin, cephalin, phosphatidylethanolamine, and also of fatty acids of atheroma has been noted by Bowyer and associates, and this similarity and the dissimilarity between the rat and these species in these lipids pattern of their arterial wall have been presumed by them to originate from the difference of enzymes.

This peculiar similarity between man and rabbit in these chemical and morphological aspects of arterial wall and atheroma led us to use mainly the rabbit for the search of antiatherosclerotics.

Existence of histamine-type leakage in vasa vasorum. Majno and colleagues[14,15] discovered the opening of endothelial gaps by endogenous inflammatory sub-

Fig. 5. Vasa vasorum of the aortic walls (longitudinal sections) in rabbit (A) and dog (B).

stances in rat scrotum and they clarified the leakage of plasmal fluids, large particles, and formed elements from capillaries and venules into the extravascular spaces through gaps opened by endogenous inflammatory substances. They called this phenomenon the "histamine type leakage" because it was induced by local application of histamine and serotonin. They also believed these inflammatory substances attack endothelial cells, inducing the swelling which causes the separation of neighboring endothelial cells from each other and thus opening endothelial gaps. We also found the histamine type leakage in vasa vasorum of aortas of rabbit, dog,[6] monkey and man showing the edematous change. Actually, in the endothelial cells of the capillaries of vasa vasorum of rabbits, dogs, monkeys, and men we observed two kinds of so-called tonofilaments: the one is myosinlike filament with the diameter of 100 Å and another one is actinlike filament with that of 50Å, which show close morphological similarity to contractile myofilaments of smooth muscle cells. The richness in tonofilaments and pinocytotic vesicles is also a characteristic feature of the endothelial cells of capillaries of vasa vasorum.

The histamine-type leakage was also induced with bradykinin by Schachter[19] and by Rowley[20] and also with lysylbradykinin by us.[21] Rowley[20] clarified the importance of venoconstriction in the histamine type leakage and has shown experimental evidence of this. The dose-dependent venoconstrictive effect of endogenous inflammatory substances was found by us in saphenous[22,23] and marginal ear[24] vein preparations of rabbits and coronary vein preparations of dogs.[25] Among endogenous venoconstrictive substances, bradykinin exhibits the most potent venoconstrictive effect and its tachyphylaxis was often characteristically weak, while serotonin, histamine, and adrenaline show a venoconstrictive effect, their tachyphylaxis is remarkably strong.

Since the discovery of the specific digital vascular response of man[26] to intra-arterial injection of bradykinin, much attention has been directed to the pathophysiological significance of bradykinin and its active homologues in various clinical problems.[27,28]

Nevertheless, the swelling of endothelial cells and venoconstrictive effect seem to contribute to the opening of endothelial gaps resulting in the histamine type leakage.[18]

Edematous arterial reaction and a special property of cholesterol and other atherogenic factors (bradykinin hypothesis). In his analysis of atherogenesis from cholesterol the author[29,30] found a special property of cholesterol. When it was given orally to rabbits in a dose of 1 Gm. per kilogram, the walls of arteries exhibited an edematous swelling starting 15 to 30 minutes after administration and disappearing 6 to 8 hours thereafter. The edematous feature is stronger in the subendothelial space and the innermost layers of media as compared with the outer layers of media.

Electron-microscopic analysis[31] has revealed the enlargement of amorphous extracellular spaces due to accumulation of serous substances, which seemed to come from vasa vasorum, though not all.

In vasa vasorum the pores of endothelial cells of capillaries are thought to be an important pathway, because rabbit and man, which have specifically such visceral type capillaries in vasa vasorum, seem specifically to tend to the edematous arterial reaction. During the edematous

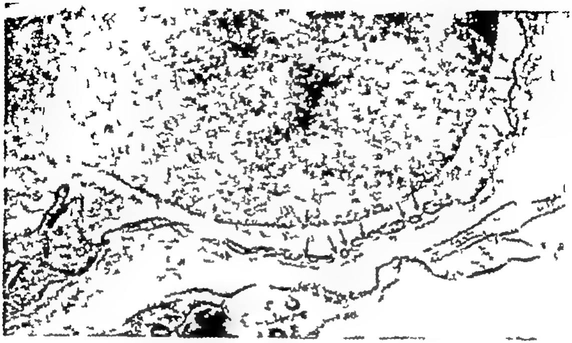

Fig. 4. Porous capillaries of atheromatous lesions of man (arrows show pores).

reaction the opening of endothelial gaps in capillaries and venules of vasa vasorum was also found and the pinocytotic activity seemed to be stimulated in endothelial cells of capillaries and venules of vasa vasorum while the pinocytotic activity of the endothelial cells of arterial lumen seemed not to be increased.

Simultaneously with the appearance of the edematous arterial reaction several hematological changes take place. The one-stage prothrombin time, Lee-White time and Stypven time shorten concomitantly and transiently,[30,32] while the adhesive-platelet count also shows a concomitant and transient reduction.[30,32] These findings suggest the possibility that oral administration of cholesterol may induce an activation of Hageman factor as in the case of saturated fatty acids as shown by Margolis,[33] who has also shown that the activation of Hageman factor[34,35] not only initiates the blood clotting reaction but also activates the bradykinin-forming enzyme resulting in the production of bradykinin.

Actually the bradykinin-forming enzyme inhibiting substances such as glucocorticoids,[36] trasylol and soybean trypsin inhibitor have exhibited an unmistakable preventive effect against the edematous arterial reaction induced by cholesterol. Also the venous bradykinin antagonistic substances such as pyridinolcarbamate,[22,26,27] nialamide, cyproheptadine,[7,18] aminopyrine,[7] and estrogens,[29] including their active derivatives, exhibited an inhibitory effect.

Nevertheless the edematous arterial reaction[22] has been induced by oral administration of cholesterol, animal fats and saturated fatty acids, although not by vegetable oils or unsaturated fatty acids, carbohydrates such as starch or glucose, or proteins such as casein. Specifically the atherogenic substances seem to induce the reaction. Moreover epinephrine, traumatic stress, smoking, and substances of high molecular weight injected intravenously induce the edematous arterial reaction accompanied by similar hematological changes, and they are also known to promote or establish atheromatous lesions.

According to Rocha e Silva,[19] epinephrine is presumed to activate bradykinin-forming enzymes in the blood, and traumatic stress as well as the intravenous injection of substances of high molecular weight have been known to liberate epi-

Fig. 7. Porous capillaries of atheromatous lesions of rabbit (arrows show pores).

nephrine and also to activate the clotting factors including Hageman factor[22-24] which activates the bradykinin-forming enzyme. Also, the above mentioned bradykinin-forming enzyme inhibiting substances and venous bradykinin antagonists inhibited the edematous arterial reaction induced by these challenges.

Prevention of edematous arterial reaction and experimental atherosclerosis induced by cholesterol with anti-bradykinin agents. It is apparent that so-called atherogenic substances and procedures produce the edematous arterial reaction and the facts cited above suggest that the reaction is produced by bradykinin or similar active substances released by atherogenic agents. Kinins possibly increase the inflow of plasmal substances, including cholesterol-bearing high molecular weight compounds such as lipoprotein, into the arterial wall; the effect could be produced by increasing the infiltration through endothelial pores due to the increase in internal pressure of capillaries by kinin-induced arteriole dilation and/or venoconstriction and opening endothelial gaps as well as by stimulating the pinocytotic activity of endothelial cells of vasa vasorum. There is no doubt that such a condition also aggravates established atheromatous lesions rich in vascularization from vasa vasorum. It should be noted that the growing capillaries in atheromatous lesions of man and rabbit have not only endothelial cells with numerous pores (Figs. 6 and 7), but also often lack the endothelial lining; the basement membrane alone composed the capillary wall in such areas. Such a condition undoubtedly leads to leakage by increase in the intracapillary pressure. In addition, the appearance of polymorphonuclear leukocytes, known to release bradykinin-forming enzyme,[41, 42] is common finding in atheromatous lesions.[43]

It should also be noted that the arterial wall is in a state of ceaseless pulsation and exposed to all noxious agents entering the blood from the external environment, that the wall is thus prone to injuries markedly aggravating atherosclerosis has been well documented by Constantinides[4] and others through experimental evidence. Needless to say, the injury of most cells and the production of rough surface[24] are thought to release bradykinin-forming enzyme which produced bradykinin.

It is presumed that the edematous arterial reaction as well as the progress of atherosclerosis can be halted by reduc-

ing the transportation of plasmal substances into the arterial wall a process which is possibly enhanced by bradykinin and its active homologues.

Actually estrogens,[43, 4] nialamide, cyproheptadine[17, 43] and pyridinolcarbamate[17-46] antagonize the vascular permeability increasing effect and venoconstrictive effect of bradykinin [27] and act to prevent the edematous arterial reaction induced by various challenges.[7-20] All these chemical substances also exhibited a preventive effect against atherosclerosis in cholesterol fed rabbits.[21, 31]

Prednisolone and dexamethasone[1, 7] have been shown to prevent the edematous arterial reaction in doses presumed capable of inhibiting the bradykinin forming enzyme activity in animals.[30] In our recent experiments with cholesterol fed rabbits, prednisolone in such doses exhibited a powerful preventive effect against the appearance of atherosclerosis, despite the fact that the blood cholesterol level of rabbits receiving prednisolone exceeded 3 000 mg 100 ml double that of the placebo control group and these data agree entirely with Oppenheim and Bruger.[33] In addition in our rabbits receiving 1 mg per kilogram of prednisolone there were almost no atheromatous lesions, and the cholesterol content of the aortic wall remained almost within the normal ranges, while there were severe atheromatous lesions in the placebo control group It should also be noted that the animals of prednisolone group exhibited a severe accumulation of cholesterol in the lipid storing or synthetizing organs such as liver or adrenals showing a highly interesting contrast to such a minimal or almost no accumulation of cholesterol in their arterial walls. This evidence suggests the difference in the mode of accumulation of cholesterol between the arterial wall and the organs that store or synthesize lipids.

The most potent antiatherosclerotic property of this hypercholesterolemic (not hypocholesterolemic) and bradykinin forming enzyme inhibiting substance may suggest the importance of kinins in atherogenesis, because kinins are presumed to be released through activation of Hageman factor by cholesterol given orally and to represent the vascular permeability increasing property of cholesterol itself[19] in the arterial wall Prevention of the leakage[17] is believed not only to stop atheromatous changes and to prevent the thrombotic complication but also to improve conditions by absorbing and removing atheromatous substances including cholesterol

In our work with experimental animals, this belief was found to be correct. Actually the atherosclerosis produced in rabbits by feeding them 1 per cent cholesterol pellets for 15 weeks responded to treatment with pyridinolcarbamate[11, 22] in a daily oral dose of 10 to 30 mg per kilogram for 10 to 30 weeks The cholesterol content of atheromatous aortic wall exhibited a gradual and statistically significant decrease under pyridinolcarbamate treatment as compared with placebo control animals.

Duguid's hypothesis The European group[4] seems to agree that thrombotic deposits lining the blood vessel can be incorporated into the vessel wall thus forming atherosclerotic lesions.

However it has not been agreed that this is the mechanism that initiates atherosclerosis. In the edematous arterial reaction induced by atherogenic substances,[19-22] the adhesiveness of endothelial lining to platelets and leukocytes appears concomitantly with reduction in adhesive platelet count and the reduction of one stage prothrombin time, and represents a thrombotic tendency Such a reaction of the arterial wall seems to initiate not only mural thrombi but also atherosclerosis with or without the mechanism of mural thrombosis, and the substances capable of preventing such reactions are considered to be antiatherosclerotic as in the case of *pyridinolcarbamate*

Prevention of human atherosclerosis apoplexy and myocardial infarction Constantinides[49] identified breaks in endothelial lining covering the atheromatous plaque as the origin of fatal thrombosis in victims of apoplexy and myocardial infarction and explained that the rough surface of the broken area activates the clotting factor As a cause of breaks in endothelial lining the author has proposed the acute enlargement of plaque or the appearance of digestive enzymes due to leakage from the vascular plexus at the base of atheromatous plaque.

On such an assumption the use of a sub-

stance to prevent the edematous arterial reaction seems promising Specifically the leakage could be reduced by substances such as estrogens or pyridinolcarbamate in dosages tolerable to the endothelial lining and thus, the breaks would be prevented Actually estrogens[61 62] and pyridinolcarbamate[63] have been shown to reduce significantly the relapse rate in apoplexy and myocardial infarction.

Needless to say estrogen has been known to show a seemingly beneficial effect on the lipid content of the blood However the effect is relatively weak, and Pick[64] and Furman and associates[65] agree that this characteristic is not solely responsible for its antiatherosclerotic quality

The treatment of human atherosclerosis Scar is not subject to drug therapy but atheromatous lesions should be cured Until recently no suitable substance has been available for the treatment of atheromatous lesions themselves.

In the pregnant women especially during the latter half of pregnancy[66] large amounts of estrogens are produced in adrenal glands of the fetus and in the placenta. Such quantities of estrogens, translated roughly in terms of our experience with rabbits, seem to constitute a dosage adequate for curing atheromatous lesions. Estrogens in such large amounts are tolerable only for pregnant women and seem to be a providential antiatherosclerotic for the mother of her child. However the dose of estrogens allowable for men and nonpregnant women is limited to a few milligrams because of their feminizing and other effects.

In contrast pyridinolcarbamate shows a clear-cut curative effect in daily doses of 10 to 30 mg per kilogram in rabbits, and such doses per kilogram have been well tolerated by a large number of men and women over a period of years. The attempt to treat human atherosclerosis with pyridinolcarbamate the first synthetic antikinin-antiatherosclerotic, was an exciting one but a careful clinical pharmacological approach has been *maintained* since the beginning[53,57] Among atherosclerotic diseases, patients suffering from atherosclerosis obliterans offer a good opportunity for study because their arterial pulsation arterial blood flow and ischemic disorders of affected arteries of the end organs can be observed directly[57] The impaired arterial pulsation and arterial blood flow as well as the low temperature cyanosis rubor ulcer and gangrene of affected extremities due to insufficiency of arterial blood supply of atherosclerotic arteries, have provided reliable objective signs for the evaluation of drugs. Using such criteria, clinical-pharmacological methods[57] have been applied successfully under the double blind method. The results obtained have suggested the possibility of treating symptomless atherosclerosis, common among the people of the world with antibradykinin agents such as pyridinolcarbamate.

Conclusion

The reason why the microcirculatory aspect of atherogenesis has been the main subject of this article is the peculiarity of *the arterial wall* of man. The capillaries of vasa vasorum often have pores representing visceral type and such fenestrated capillaries of vasa vasorum are seen commonly in man and rabbit among animals tested and the arterial walls of both species prone to the infiltration of serous substance including cholesterol and to atherosclerosis.

Another reason is the results in the treatment of atherosclerosis with the first synthetic antikinin-antiatherosclerotic.[11 53,57 63]

Needless to say the chemical aspect of atherogenesis is obviously important, not only in lipid metabolism but also in kinin formation[68] and inactivation as well as interaction of lipid metabolism and various inflammatory substances

REFERENCES

1. Adams, C W M Atheroma lipids, J Atheroscler Res. 7 117 1967
2. Newman, H A I McCandless, E. I and Zilversmit, D B The synthesis of ^{14}C-lipids in rabbit atheromatous lesions, J Biol. Chem. 236 1264, 1961
3. Stein, O Salinger Z., and Stein, Y Incorporation of 1-^{14}linoleic acid into lipids of human umbilical arteries, J Atheroscler Res. 3 189 1963.
4. Lofland, H B, Lipid metabolism in pigeon aorta during atherogenesis, J Lipid Res. 6 112 1965
5. Chartman, B and Lipsky S. R., Study on the movement in vivo and in vitro of labelled cholesterol across the aorta of the normal rat, J Atheroscler Res. 7 143 1967
6. Splant, R. C. and Galambos, J T., Autoradio-

graphic demonstration of ingested cholesterol-4-C^{14} in the normal and atheromatous aorta, Am. J. Path. 41:877, 1964.
7. Clarke, J. A.: An x-ray microscopic study of the vasa vasorum of the normal human thoracic aorta, Z. Anat. Entwickl. Gesch. 124:261, 1964.
8. Clarke, J. A.: An x-ray microscopic study of the vasa vasorum of the normal human ascending aorta, Brit. Heart J. 27:99, 1965.
9. Sunaga, T., Sasaki, T., and Shimamoto, T.: Demonstration of vasa vasorum in the inner most layers of media of dog aorta and their leakage—Studies on the edematous arterial reaction, Jap. Circulation J. 31:339, 1967.
10. Shimamoto, T.: A anti-atherosclerotic, pyridinolcarbamate, Asian M. J. 10:423, 1967.
11. Bej, M. L. M., and Tavares, J. F.: Vasa vasorum terogénese, Folia Anatomica Universitatis Conimbrigensis 36:1, 1966.
12. Bennett, H. S., Luft, T. H., and Hampton, J. C.: Morphological classification of vertebrate blood capillaries, Am. J. Phys. 196:381, 1959.
13. Fawcett, D. W.: Comparative observations on the fine structure of blood capillaries, *in* Smith, D. E., and Orbison, J. L., editors: The peripheral blood vessels, Baltimore, 1963, The Williams & Wilkins Co., p. 17.
14. Bowyer, D., Howard, A. N., Gresham, G. A., Bates, D., and Palmer, B. V.: Aortic perfusion in experimental animals. A system for the study of lipid synthesis and accumulation. Internat. Symposium on recent advances in atherosclerosis, Athens, May 30 to June 2, 1966.
15. Majno, G., and Palade, G. E.: Studies on inflammation. I. The effect of histamine and serotonin on vascular permeability: an electron microscopic study, J. Biophys. Biochem. Cytol. 11:571, 1961.
16. Majno, G., Palade, G. E., and Schoefl, G. I.: Studies on inflammation. II. The site of action of histamine and serotonin along the vascular tree. A topographic study, J. Biophys. Biochem. Cytol. 11:607, 1961.
17. Shimamoto, T., Sunaga, T., Sasaki, T., Kubota, A., Matsumura, T., and Ishioka, T.: Possible significance of bradykinin as genesis of arteritis and atherosclerosis, International Symposium on vasoactive polypeptides: bradykinin and related kinins, Ribeirão Preto, III International Pharmacological Congress and Soc. Bras. Farmacologia Terapêutica Experimental, São Paulo, 1967, p. 267.
18. Sasaki, T., Sunaga, T., and Shimamoto, T.: Demonstration of vasa vasorum in the inner most layers of media of dog aorta and their vascular leakage. Studies on the edematous arterial reaction, Jap. Circulation J. 31:347, 1967.
19. Schachter, M.: Bradykinin and other capillary active factors, First Internat. Pharmacol. Meet. 9:187, 1961.
20. Rowley, D. A.: Venous constriction as the cause of increased vascular permeability produced by 5-hydroxytryptamine, histamine, bradykinin, and 48/80 in the rat, Brit. J. Exper. Path. 45:56, 1964.
21. Sunaga, T., Sasaki, T., and Hiramoto, Y.: Vascular leakage by bradykinin or lysylbradykinin and preventive effect by pyridinolcarbamate, Ochanomizu J. 13:121, 1965.
22. Shimamoto, T., Numano, F., Fujita, T., Ishioka, T., and Atsumi, T.: Treatment of experimental and human atherosclerosis with pyridinolcarbamate, Asian M. J. 8:12, 1965.
23. Ishioka, T., Matsumura, T., Takeuchi, K., Yagishita, M., and Hazama, H.: Studies on venoconstriction effect of venoactive substances on saphenous vein of rabbit and antagonists of venoconstriction induced by bradykinin, Ochanomizu M. J. 13:360, 1965.
24. Hazama, H.: Effect of endogenous vasoactive substance on marginal vein of isolated rabbit ear, Ochanomizu M. J. 13:359, 1965.
25. Sunaga, T., Sasaki, T., Hiramoto, Y., and Tanaka, M.: Constrictive effect of kinins on coronary vein and antagonistic effect of pyridinolcarbamate, Ochanomizu M. J. 13:360, 1965.
26. Burch, G. E., and DePasquale, N. P.: Bradykinin, digital blood flow, and the arteriovenous anastomosis, Circulation Res. 10:105, 1962.
27. Burch, G. E., and DePasquale, N. P.: Bradykinin, Am. Heart J. 66:116, 1963.
28. Webster, M. E.: The kallikrein-kininogen-kinin system, Arthritis & Rheumatism 9:473, 1966.
29. Shimamoto, T., and Sunaga, T.: Edematous arterial reaction by adrenaline and cholesterol and its prevention by MAO inhibitor observed by electron microscopic technique, Jap. Heart J. 3:581, 1962.
30. Shimamoto, T.: The relationship of edematous reaction in arteries to atherosclerosis and thrombosis, *J. Atheroscler. Res.* 3:87, 1963.
31. Shimamoto, T.: Acute vascular reaction in regard to atherosclerosis, Asian M. J. 4:809, 1961.
32. Shimamoto, T., Maezawa, H., Yamazaki, H., Ishioka, T., and Fujita, T.: Edematous arterial reaction and its relationship to atherosclerosis and thrombosis, *in* Bajusz and Jasmin, editors: Meth. Achievm. Exp. Path. Basel, 1966, S. Karger, vol. 1, p. 337.
33. Margolis, J.: Activation of Hageman factor by saturated fatty acids, Australian J. Exper. Biol. 40:505, 1962.
34. Margolis, J.: The mode of action of Hageman factor in the release of plasma kinin, J. Physiol. (London) 151:238, 1960.
35. Margolis, J.: The interrelationship of coagulation of plasma and release of peptides, Ann. New York Acad. Sc. 104:133, 1963.
36. Cline, M. J., and Melmon, K. L.: Plasma kinins and cortisol: possible explanation of the anti-inflammatory action of cortisol, Science 153:1135, 1966.
37. Shimamoto, T., Maezawa, H., Yamazaki, H., Atsumi, T., Ishioka, T., and Sunaga, T.: Pyridinolcarbamate, a bradykinin antagonist in veins, Am. Heart J. 71:3, 297, 1966.
38. Rocha e Silva, M., and Leme, J. G.: Antagonists of bradykinin, Med. Exper. 8:287, 1963.
39. Shimamoto, T., and Ishioka, T.: Venous bradykinin-antagonistic property of estrogen, Proc. Japan Acad. 43:4, 1967.
40. Rocha e Silva, M.: Chemical mediators of the

acute inflammatory reaction, Ann. New York Acad Sc. 116:899 1964.
41 Greenbaum, L. M and Kim, K. S The kinin-forming and kininase activities of rabbit poly morphonuclear leucocytes, Brit. J Pharm. Chem 29:238, 1967
42. Zachariae, H Malmquist, J and Oates, T A. Kinase in human polymorphonuclear leucocytes, Life Sc. 5:2347 1966.
43 McGill, H. C., J Geer J C., and Strong J P in Sandler M., and Bourne, G. H editors Natural history of human atherosclerotic lesions, atherosclerosis, and its origin, New York and London, 1963 Academic Press, p. 39
44 Constantinides, P Experimental atherosclerosis, Anat. Rec. 146:219 1963. Elsevier Publishing C Amsterdam, London, New York, 1965 p 49
45 Bonta, I L., and de Vos, C. J The effect of estriol 16, 17-dihemisuccinate on vascular permeability as evaluated in the rat paw oedema test, Acta endocrinol 49:403, 1965
46. Bonta, I L., and de Vos, C. J Antihemorrhagic and permeability inhibitor effect of estriol and estiol-16, 17-disodium succinate in animal experiments In "2nd international conference on angiology Darmstadt, 1962, 1963 Steinkopff Verlag pp. 274-275
47 Yamazaki, H., Sano, T and Odakura, T Antagonistic substances against increase in permeability of skin vessels induced by bradykinin, lysylbradykinin, kallikrein, histamine, and serotonin, Ochanomizu M J 13:361 1965
48. Iwakane, N Inhibitory effect of oral pretreatment with pyridinolcarbamate and cyproheptadine on increased capillary permeability induced by intradermal injection of bradykinin, lysylbradykinin, kallikrein, histamine, and serotonin in guinea pigs, Ochanomizu M. J 13:363 1965
49 Yamashita, S. Study on vascular permeability increasing effect of bradykinin and preventive effect of pyridinolcarbamate, Ochanomizu M J 13:363 1965
50. Sunaga, T Sasaki, T Hiramoto, Y and Tanaka, M. Vascular leakage by bradykinin or lysylbradykinin and preventive effect by pyridinolcarbamate, Ochanomizu M J 13:364, 1965
51 Shimamoto, T Sunaga, T Sano, T Yagishita, M and Hiroki, T Search for atherogenic and antiatherogenic substances, Circulation 24 1104 1961
52. Adams, C. W M Bayliss, O B., and Ibrahim M Z. M Effect of nialamide on cholesterol-induced atheroma in the rabbit J Atheroscler Res. 2:493, 1962.
53. Shimamoto, T Numano, F and Fujita, T: Atherosclerosis-inhibiting effect of an antibradykinin agent, pyridinolcarbamate, Am. Heart J 71:216, 1966.
54 Numano, F The prevention of atherosclerosis by pyridinolcarbamate in cholesterol-fed rabbits, abstract from J Jap Soc. I t. Med. 54 1260, 1966.
55 Pick, R., Stamler J Rodbard, S., and Katz, L. N The inhibition of coronary atheromatosis in cholesterol-fed chicks receiving estrogens, Circulation 4:468, 1951
56. Pick, R., Stamler J Rodbard, S., and Katz, L. N Estrogen induced regression on coronary atherosclerosis in cholesterol fed chicks, Circulation 6:460 1952.
57 Malinow M R., Pellegrino, A. A. and Ramos, E. H. Prevention of aortic atheroscleroma in rabbits by intravenous microcrystalized estradiol Benzoate and Dextran, Proc. Soc. Exper Biol. & Med. 97:446, 1958.
58. Oppenheim, E., and Bruger M The effect of cortisone and ACTH on experimental cholesterol atherosclerosis in rabbits, Circulation 6:470, 1952.
59 European atherosclerosis group, symposium on Duguid' hypothesis, Bull. Swiss Acad. M. Sc. 22 1 1966.
60. Constantinides, P Plaque fissures in human coronary thrombosis, J Atheroscler Res. 6 1 1966.
61. Rivin, A. V and Dimitroff S P The incidence and severity of atherosclerosis, Internat. symposium on recent advances in atherosclerosis, Athens, May 30 to June 2, 1966.
62. Robinson, R. W Survival after cerebral thrombosis, Int. symposium on recent advances in atherosclerosis, Athens, May 30 to June 2 1966.
63 Yamazaki, H Murase, H Shimamoto, T J Honda, Y Katsu, K., Hentona, M Odakura, T Takeuchi K., and Shimamoto, T Pyridinolcarbamate on the relapse rate of cerebral apoplexy Clin. Neurol. 7:310, 1967
64. Pick, R. Estrogens and atherosclerosis, Internat. symposium on recent advances in atherosclerosis, Athens, May 30 to June 2, 1966.
65. Furman, R. H., Alaupovic, P Bradford, R. H and Howard, R. P Gonadal hormones, blood lipids and ischemic heart diseases, Internat symposium on recent advances in atherosclerosis, Athens, May 30 to June 2, 1966
66. Randsen, V A. The excretion of oestriol in normal human pregnancy Copenhagen. Munksgaard, 1965 cit from estrogen assays in clinical medicine, edited by Paulsen, C. A. Seattle, University of Washington Press, 1965 p. 234
67 Hill, A. B Principles of medical statistics, London, 1966, Lancet Limited
68. Eisen, V and Keele C. A Possible modes of kinin formation in some pathological states in man, Biochem. Pharmacol. 11 1390, 1965
69 Erdos, E. G and Yang H. Y T Inactivation and potentiation of the effects of bradykinin. Hypotensive peptides, edited by Erdos, Back, and Sicuteri, New York, 1966, Springer Verlag p. 235.

Fundamentals of clinical cardiology

Newer concepts in the genesis of cardiac arrhythmias

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Cardiac arrhythmia or any departure from normal cardiac rhythmicity may interfere with the physiological performance of the heart. The discussion of arrhythmias must then begin with a definition of normal cardiac rhythmicity. Ordinarily, impulse formation is initiated in the sinoatrial (S-A) nodal region. The optimal rate of the S-A nodal discharge is between 60 and 100 per minute in an adult. The rhythm must be reasonably regular. Although no specific limit can be set, fluctuations of more than 0.16 sec. among cycle lengths in a steady state are usually regarded as sinus arrhythmia. Furthermore, the entire heart must respond to every sinus impulse with a normal time course of activation. Thus, an S-A nodal discharge is always followed by sequential excitation (and contraction) of the atria and the ventricles with an optimal and constant atrioventricular (A-V) conduction time. Normal A-V conduction time, expressed by the P-R interval of the electrocardiogram (ECG), ranges from 0.12 to 0.21 sec. in an adult. Accordingly, any change in the origin of impulse formation, the rate, regularity, or the sequence of atrial and ventricular excitation can lead to various types of cardiac arrhythmias.

For clinical purposes, classification of cardiac arrhythmias is usually based on the origin of impulses (supraventricular or ventricular) and their mode of appearance (premature systole, tachycardia, flutter, fibrillation, etc.). However, as cardiac rhythmicity depends on the electrophysiological properties of individual heart fibers, the genesis of arrhythmias should be discussed with reference to cellular physiology.[1-4]

From the electrophysiological standpoint, genesis of cardiac arrhythmias is often divided into two major categories, or (1) disturbances of impulse formation and (2) disturbances of conduction. However, there are certain mechanisms which cannot easily be classified into either of these two types, and arrhythmias caused by (3) combined disturbances of impulse formation and conduction are also recognized. In this review, a detailed discussion of the pertinent electrophysiologic mechanisms will be presented (Table I).

Disturbances of impulse formation

Automaticity. The term automaticity refers to the ability of certain cardiac fibers to generate an impulse of their own. Under appropriate conditions, a single fiber of this type is able to discharge itself without any extrinsic stimuli. Automaticity appears to be characteristic of the specialized cardiac fibers, which are found in the

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Table I

I Disturbances of impulse formation
- A Automaticity
  - 1 Physiologic alterations
  - 2 Enhanced automaticity
  - 3 Depressed automaticity
- B Other mechanisms of impulse formation
  - 1 Oscillation
  - 2 Afterpotentials
  - 3 Local potential difference
    - a. Asynchronous repolarization
    - b. Partial depolarization

II Disturbances of impulse conduction
- A. Simple conduction block
  - 1 Refractory tissue
    - a Dissimilar action potential duration and excitability between fiber types
    - b Interference of two impulses
  - 2. Decremental conduction
  - 3 Inhomogeneous conduction
- B Unidirectional block and re-entry
  - 1 Unidirectional block and re-entry in the A-V junction
  - 2 Local block and microre-entry

III Combined disturbances of impulse formation and conduction
- A. Parasystole
- B Ectopic rhythms with exit block

IV Fibrillation

S-A node intra atrial conducting system A-V node His bundle bundle branches and peripheral Purkinje system On the other hand ordinary atrial and ventricular fibers do not possess automaticity and are called nonspecialized myocardial fibers.

It is well known that every cardiac fiber similar to other excitable tissues such as nerve or skeletal muscle, is surrounded by a polarized membrane with the cell interior negatively charged during the resting state When a current flow across the cell membrane brings the transmembrane potential to its threshold level the fiber usually undergoes a rapid reversal of polarity or depolarization and the cell is excited In nonspecialized fibers the negative transmembrane potential during the resting state (resting potential) remains constant and its shift to the threshold potential is caused by a propagated wave of excitation. Contrarily an automatic fiber can spontaneously and gradually lose its resting potential to reach the threshold level as illustrated in Fig 1 This gradual decrease in the resting potential is called diastolic depolarization which is the actual mechanism of automaticity

Following complete activation of the entire cardiac musculature slow diastolic depolarization could simultaneously proceed in various specialized tissues However the slope of diastolic depolarization is usually steepest in fibers of the S-A node Hence some of the S-A nodal fibers attain threshold potential prior to any other automatic fibers and the impulse thus generated is propagated to the entire heart to control cardiac rhythmicity In this manner the S-A node acts as the normal and usually dominant pacemaker of the heart and the rhythm is called sinus rhythm On the other hand other automatic fibers may sometimes control the cardiac rhythm and are often termed latent pacemakers.

Factors which modify the cycle length of an automatic fiber are also illustrated in Fig 1 The most important determinant is the slope of diastolic depolarization An increase in the slope of diastolic depolarization in S-A nodal fibers will bring the transmembrane potential to the threshold more rapidly and accelerate the sinus rhythm Sinus tachycardia seen under various conditions is usually the result of this mechanism The second factor is the difference between the threshold potential and the maximal diastolic potential attained at the end of repolarization Acetylcholine increases this potential difference by increasing the maximal diastolic potential (hyperpolarization) in the S-A node At the same time this agent markedly decreases the slope of diastolic depolarization It is the combination of these two changes which causes sinus bradycardia or even sinus arrest following vagal stimulation Fluctuation in vagal tone associated with the respiratory cycle is a common cause of sinus arrhythmia A different type of altered S-A nodal rhythmicity called ventriculophasic sinus arrhythmia,[8] deserves comment. This arrhythmia is often observed in the presence of a regular 2:1 A-V block or high grade A-V block, and is characterized by a shortening of the cycle length which contains a ventricular contraction. As the sinus node artery usually penetrates the S-A nodal tissue

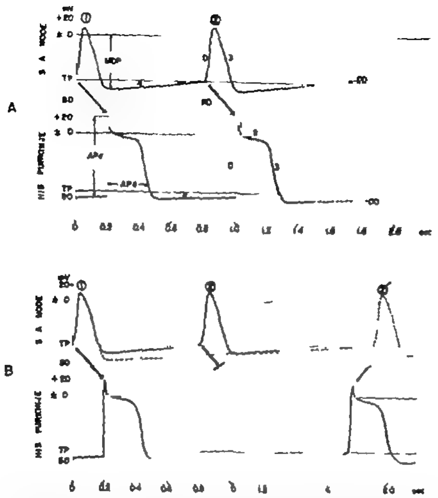

Fig. 1. Transmembrane potentials of the S-A nodal and His-Purkinje fibers are schematically shown. A. The slope of diastolic (phase 4) depolarization (*DD*) is greater and the threshold potential (*TP*) is attained earlier in the S-A nodal fiber than in the His-Purkinje fiber. The sinus node fires a second impulse after 0.8 sec. or at the rate of 75 per minute. The His-Purkinje system is discharged by propagated sinus impulses (arrows). Note differences in the action potential amplitude (*AP*), the action potential duration (*APd*), the rate of depolarization (*RD*) or steepness of phase 0, and the time course of repolarization (phases 1, 2, and 3) between the two fiber types. *MDP*, Maximal diastolic potential. *B*. When a second sinus impulse *two* fails to reach the *His-Purkinje* system due to S-A or A-V conduction block (blocked arrow) or when the sinus rate is markedly slowed by *vagal stimulation* (with increased maximal diastolic potential and decreased slope of phase 4 depolarization as shown by the dotted line), diastolic depolarization of the His-Purkinje fiber could proceed to attain the threshold potential and cause an escape beat. Note smoother transition from phase 4 to phase 0 and slightly reduced rate of depolarization with spontaneous discharge of the *His-Purkinje system.*

ventricular contraction and resultant phasic flow in this artery may in some way affect the automaticity of this node. The slope of diastolic depolarization in the S-A nodal and Purkinje fibers has been shown to increase on stretching of these tissues.[7] As dilatation of the sinus node artery is accompanied by a bradycardia[8] and constriction by a tachycardia, ventriculophasic sinus arrhythmia may be related to a change in diastolic depolarization caused by the successive dilatation and constriction of this artery with ventricular systole. Clarification of this mechanism awaits further studies.

On the other hand, shift of the pacemaker from the S-A node to other specialized fibers with less automaticity may result from a sinus slowing, as a "latent" pacemaker now finds enough time to continue its slow diastolic depolarization until the threshold is reached. Such pace-

maker shift is often seen in the presence of marked sinus arrhythmia S-A block, A V conduction block vagal stimulation or following an atrial premature systole (Fig 1) These beats are called A V nodal or junctional escape beats Automatic fibers found in the atrial tissues other than the S-A node include fibers along the junction of great veins with the right atrium fibers in and around the orifice of the coronary sinus or the circumference of the right atrioventricular ring and those in the interatrial septum and Bachmann's bundle [11] When some of these fibers possess a similar slope of diastolic depolarization as the S-A node a smooth and gradual shift of the pacemaking region between these fiber groups may cause wandering of pacemaker without significant alterations of the cycle length This possibility has been demonstrated experimentally between the S-A node and certain areas of the A V junction [12,13]

Several types of A V nodal rhythm with dependent activation of the atria and the ventricles have been shown to originate from automatic fibers located in specific regions of the A V junction [13] Relative conduction times from this pacemaker to the atria and the ventricles produce various sequences in the appearance of atrial and ventricular excitation compatible with coronary sinus rhythm as well as upper or middle nodal rhythm These aforementioned variations of cardiac rhythmicity represent a physiological mechanism although they are considered some form of cardiac arrhythmia.

On the other hand if the slope of diastolic depolarization in automatic fibers outside the S-A node becomes abnormally steep these fibers may eventually take over the control of the atrial and or ventricular excitation. This is known as ectopic impulse formation due to enhanced automaticity The resultant rapid rhythm can be identified depending upon the location of the pacemaking fibers as atrial A V junctional or ventricular tachycardia Automatic fibers found in the ventricles belong to the specialized conducting system including His bundle bundle branches, and Purkinje fibers. Peripheral Purkinje fibers show extensive ramifications within the ventricular muscle.

Ventricular arrhythmias may result from various factors known to enhance automaticity in the His-Purkinje system Lowered extracellular potassium concentration increases the slope of diastolic depolarization and decreases the maximal diastolic potential. [1] Both factors may accelerate ectopic impulse formation Digitalis glycosides also significantly enhance automaticity in Purkinje fibers, before the transmembrane potential of ventricular muscle fibers is greatly modified [14-17] Increased frequency of discharge is also observed in the presence of catecholamines[1] or mechanical stretch.[7] Passage of weak depolarizing currents across the Purkinje fiber membrane increases the slope of diastolic depolarization [1] It is possible that electrotonic currents due to an ischemic lesion of the myocardium could similarly enhance automaticity in the adjacent Purkinje fibers.

Enhanced automaticity in ectopic sites may appear intermittently or persist for a prolonged period An ectopic pacemaker may compete with the normal S-A nodal pacemaker for control of the heart or even with a third group of automatic fibers (multifocal pacemaking activity) Nevertheless it is most likely that many instances of self-sustaining ectopic tachycardias result from increased automaticity Contrarily the role of this mechanism in the production of isolated or coupled premature beats (extrasystoles) is unknown except in the presence of a parasystolic rhythm It has been suggested that occasional failure of sinus impulses to propagate into some portions of the specialized conducting system showing diastolic depolarization may cause coupled premature systoles This last mechanism implies an associated conduction disturbance (local unidirectional block) and will be discussed later

Under certain clinical conditions depression rather than enhancement of automaticity engenders serious disturbances of cardiac rhythmicity especially when associated with disorders of A V conduction In the presence of high grade A V block some automatic fibers in the His-Purkinje system usually assume pacemaking activity to prevent prolonged periods of ventricular asystole. However

high extracellular potassium concentrations may decrease the slope of diastolic depolarization in Purkinje fibers so that threshold cannot be attained.[2] Similar specific inhibition of pacemaker activity due to high potassium has been postulated by other investigators to explain cardiac arrest occurring under this condition.[21] However, these investigators later reported another possible mechanism of arrest, i.e., an increased ventricular excitability threshold.[22] In some instances of ouabain toxicity, a decrease in the resting potential and loss of excitability in Purkinje fibers were observed.[23] This could at least theoretically result in ventricular asystole. Some statistics suggest that cardiac arrest occurs more frequently than ventricular fibrillation as a cause of sudden cardiac death following myocardial infarction. In those instances, so-called downward displacement of the pacemaker with progressive slowing of the ventricular rate often leads to ventricular standstill.[2] Whether the actual mechanism of these changes is predominantly a depression of automaticity in all the specialized fibers or is more dependent on the associated disturbance of conductivity and excitability is still unknown.

It has generally been accepted that automaticity is characteristic of specialized fiber types and ordinary atrial or ventricular fibers do not possess this feature.[3] A classical observation on the initiation of spontaneous beating by catecholamines in quiescent left atrium, where histological studies show absence of specific pacemaker tissue,[25] may not be conclusive in assigning some automatic activity to the ordinary atrial muscle. More recently, however, both atrial and ventricular fibers possessing no automaticity have been shown to develop diastolic depolarization and spontaneous firing in a potassium and calcium free perfusate.[6] Obviously, the possibility of such unphysiological situations playing a significant role in clinical arrhythmia is quite remote, even in a severely diseased heart. The suggestion that functional differentiation of cardiac muscle into automatic and nonautomatic fibers may be dependent on relative membrane conductances to potassium and sodium is an interesting challenge to the fundamental problem.[26] Data reporting higher sodium concentration in automatic cells than in ordinary myocardial cells may support this concept and further suggest the important role of various electrolytes in normal and abnormal cardiac rhythmicity.[27,28]

Other mechanisms of impulse formation. In contrast to the impulse formation due to automaticity, other mechanisms usually require an initiating beat for the generation of a new impulse. The phenomenon of oscillatory potentials in cardiac muscle was first reported in 1943.[29] Although oscillatory prepotentials of gradually increasing amplitude as well as similar afterpotentials were shown to result in a new impulse formation under abnormal conditions, the use of an extracellular type of recording limited the validity of these observations. On the other hand, recent studies utilizing microelectrode techniques more clearly demonstrated the role of oscillatory transmembrane potentials in causing spontaneous discharge of the S-A nodal and Purkinje fibers.[19,30] In the S-A node, under the influence of isoproterenol and lowered sodium concentration, a spike discharge was followed by positively damped and then negatively damped subthreshold oscillations, which often terminated in another spontaneous spike potential after varying period of time.[30] The frequency of these oscillations was similar to that of spontaneous spike discharge and appeared rather independent of the concentration of major cations. Similarly, initiation of pacemaker activity in Purkinje fibers due to low potassium solution was shown to result from increasing magnitude of oscillatory potentials reaching the threshold potential.[19] The oscillations in this instance indicated a rather slow process (1 cycle per 2 to 3 sec.), more or less comparable to the intrinsic rhythmicity of this specialized tissue. Hence, these oscillatory potentials may be related to physiological impulse formation rather than to more rapid ectopic impulse generation. In contrast, application of aconitine on ventricular fibers (or "transitional" fibers between Purkinje and ventricular) produced a positive afterpotential and subsequent oscillatory potentials with rapid rates (200

to 400 per minute) which appeared responsible for a flutter like arrhythmia in this tissue.[18]

Various afterpotentials other than oscillations comprise a second mechanism of this category. When tissues from human or chimpanzee atria were placed under hypothermia [19] the action potential plateau occurred much closer to the resting potential and lasted much longer than at physiological temperatures and a second spike discharge (or even a fully developed action potential) was frequently produced from this plateau before the completion of repolarization. The second action potential spike showed a greater amplitude and a longer duration than the spike of initial depolarization. Development of such a second discharge was accompanied by a stronger contraction. These investigators presented the following hypothesis. Under increasing degrees of hypothermia, the action potential duration becomes progressively prolonged with the plateau occurring at a progressively more negative level. Eventually at certain temperature recovery of excitability (or termination of refractory period) may occur at a time when the plateau is at a potential level very close to the threshold potential, and firing of a second response results.

Other types of afterpotentials were observed in rat or dog hearts following perfusion with veratrum alkaloids.[20] These alkaloids markedly prolonged the repolarization phase in the atrial or ventricular fibers, as much as 5 or 10 sec. During the long lasting plateau the level of which is not as negative as in the hypothermic human atria, repetitive firing of smaller action potentials or oscillations occurred. This repetitive firing gradually subsided and finally the phase 3 of repolarization terminated the long action potential.

These afterpotentials, which frequently have been invoked as a possible mechanism of coupled premature systoles [21] appear to result from altered membrane characteristics in a single fiber. However whether these afterpotentials could be, at least in part, due to certain interactions between adjacent fiber groups as exemplified in the next mechanism, will require further clarification.

The role of a local abnormal potential difference has been suggested as a third mechanism of impulse formation.[1,22,23] It has been shown that shortening of the action potential duration due to excessive digitalis glycosides may not proceed uniformly in individual fibers.[23] Localized ischemic lesions causing shortening of the action potential duration of some fibers may produce similar situations. Asynchronous repolarization may also occur when the action potential duration of certain fibers is markedly prolonged relative to that of adjacent normally repolarizing fibers. Under these circumstances an abnormal potential difference is created between contiguous fiber groups and this potential difference may re-excite the earlier repolarized and now excitable fibers to cause a second discharge. Originally this mechanism was proposed as a re-excitatory factor in the production of ventricular fibrillation.[22,23] However its possible role in the genesis of one or more premature beats is readily apparent. Probably in support of this concept is the finding that marked prolongation of the action potential duration in the S-A node due to calcium free perfusion was often followed by repetitive firing of the adjacent atrial fibers showing more rapid repolarization.[24] The production of a similar local potential difference by persistent partial depolarization of some fibers in injured cardiac muscle has also been mentioned. Although this mechanism can be considered a form of new impulse formation its distinction from re-excitation due to microre-entry is probably impossible.

Disturbances of impulse conduction

Simple conduction block. Situations where simple conduction block or failure of propagation can produce clinical varieties of cardiac arrhythmias are encountered in either the sinoatrial (S-A) or the atrioventricular (A-V) transmission. Intra-atrial or intraventricular conduction block can alter the excitation pattern in the respective chambers but usually does not cause disturbances of cardiac rhythmicity. Hence, the discussion of simple conduction block will be centered on S-A and A-V conduction.

Of various mechanisms causing failure of impulse propagation, the one most

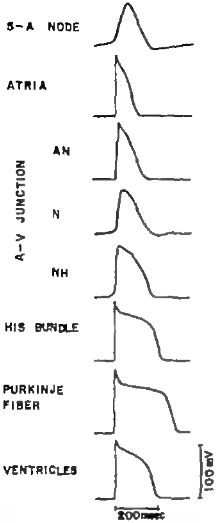

Fig 2 Characteristic action potential configurations of various fiber types. The action potential duration is progressively prolonged from the atria to the peripheral Purkinje fiber

classically invoked is the presence of refractory tissue ahead of the advancing wave of excitation This condition may occur at a junction of two fiber groups with dissimilar excitability or duration of refractoriness. It has been demonstrated that the action potential duration becomes progressively prolonged from the atrial fibers through the AN N and NH regions of the A V node,[37] His bundle, bundle branches, and to the Purkinje fibers[4] (Fig 2) Thus at any junction of two specialized conducting tissues the distal fibers usually have a longer effective refractory period and may fail to respond to high frequency of the proximal fibers.

Failure of A V conduction in the presence of extremely rapid atrial rhythms (e.g atrial flutter) or of an early atrial premature systole may occur on this basis. Complete failure of propagation of a premature atrial impulse at the level of the right bundle branch where the action potential duration is significantly longer than in the left bundle branch or in the more proximal fiber has been demonstrated[38,39] On the other hand if an impulse following upon a short cycle length arrives at the more distal fibers during their relative refractory period an action potential with a reduced rate of depolarization may cause slow decremental conduction This variety of conduction delay will be discussed later in detail

Another factor causing refractoriness or a state of nonresponsiveness in tissues ahead of the excitation front is the interference of two impulses within the A V conducting system For instance if spontaneous discharge of some automatic fibers in the A V junction occurs immediately prior to the arrival of the S-A nodal impulse to this region the sinus beat will find the pathway nonresponsive or even collide with the ectopic impulse. In this instance, neither impulse can be conducted in a forward or retrograde direction as they cancel each other Furthermore interference by return conduction (reciprocation) within the lower regions of the A V junction has been demonstrated Interfering impulses due to either automaticity or reciprocation could be concealed and may not be apparent on the clinical ECG[40]

Recently increasing attention has been given to the phenomenon of decremental conduction in cardiac tissues.[41-43] It must clearly be understood that the term decremental conduction in relation to cardiac electrophysiology implies a somewhat different phenomenon from that utilized in nerve physiology In some cardiac fiber groups, the action potential amplitude and the rate of depolarization are progressively decreased from cell to cell and the resultant stimulus becomes weaker and less effective in the course of transmission Under these conditions excitation of more distal fibers may depend on the number of participating proximal fibers. Finally the

impulse may fade out when the integrated stimulus strength becomes insufficient to cause a propagated response in more distal and still excitable fibers. These changes are most likely related to the specific membrane characteristics of these fibers, and this type of conduction is called decremental. Decremental conduction is most commonly seen in the S-A and the A-V nodes, but may also be seen in other portions of the cardiac tissue particularly in the His-Purkinje system.

In the A-V node, especially in the N region,[11] the fibers show a lower level of membrane resting potential and a significantly slower rate of depolarization than atrial or ventricular fibers, even under physiological conditions. Factors known to depress A-V conduction such as acetylcholine,[49] digitalis glycosides,[37] or lowered potassium concentration[42] tend to further decrease the rate of depolarization in these fibers and slow conduction. Varying degrees of step formation preceding the more rapid depolarization phase are commonly observed.[11, 44] Finally, the step fails to develop a full-sized action potential resulting in a local response, and propagation does not proceed more distally. Thus, an increased decrement in these regions of the A-V junction may explain some of the A-V conduction disturbances. It is to be noted that this type of conduction block is not the result of refractoriness or loss of excitability in the fibers distal to the excitation front.[42] The concept of inhomogeneous conduction is closely related to the phenomenon of decremental conduction but has certain advantages in explaining some aspects of abnormal A-V transmission. The role of decremental conduction is also suggested in S-A block.

The importance of decremental conduction in Purkinje fibers, due to either incomplete repolarization[33, 41] (during the relative refractory period) or diastolic depolarization[44] has also been emphasized. Under these circumstances, the action potential of the Purkinje fiber starts from a reduced membrane potential and shows a markedly decreased rate of depolarization as well as slow conduction velocity. Direct and indirect depression of the rate of depolarization by quinidine or high potassium concentration may have a similar effect.[47] It has been implied that a sufficient reduction in transmembrane potential can change propagation from all-or-none to decremental conduction. These observations are quite valuable in the explanation of certain clinical and experimental arrhythmias, examples of which are as follows:

1. It has been observed that the A-V nodal escape beats following a long pause often show aberrant intraventricular conduction. In contrast to aberrant conduction of atrial premature systoles with a short coupling interval, this type of aberration could not be explained by an incomplete recovery of excitability in the His-Purkinje ventricular conducting system. However, if slow diastolic depolarization of the Purkinje fibers develops during the long pause, the transmembrane potential may be significantly reduced at the time the A-V nodal escape impulse arrives at these fibers. Then the resultant Purkinje action potential will show a decreased rate of depolarization and decrement, altering the pattern of ventricular excitation.

2. It has been observed in clinical electrocardiography that a coupled premature systole more often follows an initiating beat occurring after a longer cycle length than that terminating a shorter cycle length. This phenomenon has been termed the rule of bigeminy.[41] If slow and decremental conduction is more prevalent in some peripheral ramification of the Purkinje system after a longer cycle length, there will be an increased likelihood of local unidirectional block and re-entry with the appearance of a coupled premature beat. Increased asynchrony of repolarization in ventricular fibers following a longer interval may possibly be an alternative or associated mechanism.

3. Marked degrees of decremental conduction in the His-Purkinje system may explain the genesis of peripheral types of A-V conduction block. It has been clearly demonstrated that second degree A-V block showing Wenckebach periodicity (Mobitz Type I block) is due to depression of conduction predominantly in the N region of the A-V node, while Mobitz Type II block with sudden failure of transmission usually results from conduction disturbances in more peripheral por

tions of the A-V conducting system.[40] If for some reason complete decrement of an impulse occurs in both the right and the left bundle branches simultaneously or within one bundle branch in the presence of an organic lesion and block in the other, peripheral type of A-V conduction block may result. Second degree A-V block due to excessive quinidine or high potassium concentrations has also been shown to result from propagation failure in the His-Purkinje ventricular conducting system.[42] In these instances, direct action of these agents in decreasing the rate of depolarization of the Purkinje and ventricular fibers may be the cause of decrement. As an alternative mechanism of Mobitz Type II block, the role of re-entry or reciprocation in the His-Purkinje system has been demonstrated.[48] Furthermore, it is apparent that reciprocation in these tissues may also be the result of decremental conduction.

4. Hoffman[8] has recently suggested the role of decremental conduction due to diastolic depolarization in the production of protection block around the parasystolic pacemaker.

It has been repeatedly observed that under various conditions depressing A-V transmission some A-V nodal fibers show a prominent steplike potential from which a full-sized action potential may or may not develop.[43,44,8] A larger and presumably propagated action potential appears to result from the addition of a second depolarization to the smaller or local potential change,[43] especially in the presence of block due to acetylcholine. Studies of these action potential configurations as well as relative time of activation in the nodal and His bundle fibers, under similar

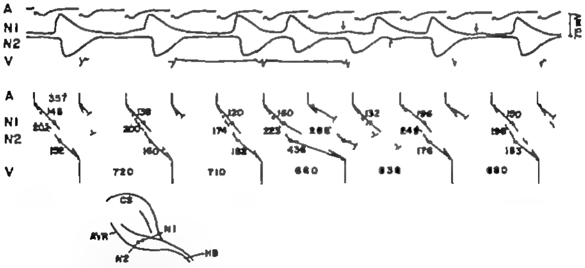

Fig. 3. Experimental record illustrating possible role of summation of excitation fronts in successful propagation during second degree A-V block in an isolated rabbit heart. *A*, Atrial electrogram. *N1* and *N2*, transmembrane potentials from two fibers located in the N region. *N2* potentials recorded with reversed polarity. *V*, Ventricular electrogram. Right atrium electrically stimulated at a constant rate. Schematic map of A-V junctional region shown at bottom. *CS*, Ostium of coronary sinus. *AVR*, fibrous atrioventricular ring; *HB*, His bundle. The Lewis type diagram illustrates sequence of excitation. Although fibers *N1* and *N2* are located close to each other and almost parallel to the direction of conduction, asynchrony of depolarization is seen between these fibers. Following four atrial beats with a 2:1 A-V response, two successive atrial impulses are conducted, the second one of which showing a reduced action potential amplitude in both fibers and a more prolonged A-V interval. The next (seventh) atrial beat produces an action potential in fiber *N2* similar in size to that in the preceding conducted beat. However, only a local response (downward arrow) is seen in fiber *N1* and excitation fails to reach the ventricles. Contrarily, the following atrial impulse (eighth) produces an action potential in fiber *N1* but only a local response (upward arrow) in fiber *N2*. Conduction to the ventricles again fails. Finally, the ninth beat is associated with more normal action potentials in both fibers and results in ventricular excitation. Hence under depressed conduction successful propagation appears to occur when two or more apparently independent wave fronts are simultaneously engaged.

conditions suggested possible fluctuation in the pathway of excitation within the A V node. We brought these points into sharp focus when we demonstrated the presence of functional longitudinal dissociation in the A V node and plotted the pathway of re-entry within this tissue.[40] Further observations on the mechanisms of second degree A V block[4] as well as supernormal conduction[48] also appear to support the concept of inhomogeneous conduction as a mechanism of various conduction disturbances seen in the A V junction Normally successful conduction through the A V nodal tissue occurs with rather synchronous activation of fibers in the AN and the N regions and a smooth excitation front invading the NH region. When the rate of depolarization is decreased and conduction further slowed particularly in the critical N region of the A V node the spread of excitation in this region becomes inhomogeneous and the resultant irregular wave front is ineffective in fully exciting the NH region.[9] A V transmission will then fail Several factors (acetylcholine digitalis glycosides low potassium concentration and probably ischemia) have been shown to depress conductivity (or increase decrement) predominantly in the N region and cause A V block.

Inhomogeneity of conduction could manifest itself as two functionally separate portions of tissue one of which shows a relatively rapid conduction velocity Increasing decrement in both portions or in the slower conducting portion alone can cause progressive fractionation of the wave front, leading to the failure of propagation Characteristic periodicity of Wenckebach phenomenon with progressive prolongation of the A V interval and eventual failure of transmission may be explained in this manner[49] On the other hand if the more rapidly conducting portion is selectively depressed by either a forward or retrograde impulse slower spread of excitation in this portion may result in a synchronized or smoother wave front. Then an unexpected successful A V or V A transmission in the presence of advanced degrees of block may ensue. This phenomenon has been described as supernormal A V conduction. In support of these hypotheses are the observations of (1) summation of impulses from divergent directions causing a greater action potential amplitude and (2) successful propagation only when several apparently independent wave fronts are simultaneously engaged[49] (Fig 3) These phenomena, which are compatible with the concept of inhomogeneous conduction are perhaps closely related to the anatomical structure of the A V node which is characterized by a complex network (with branching and anastomosing) of fibers having smaller and variable diameters.[31]

Penetration of nonconducted impulses into the A V transmission system may result from any one or combination of the factors causing conduction block (refractory tissue decremental conduction or inhomogeneous conduction) This has been designated as concealed conduction and has proved indispensable for the understanding of both simple and complex arrhythmias. Excellent clinical and experimental papers on concealed conduction have been previously published[29,53-43]

Unidirectional block and re-entry This type of conduction disturbance can be divided into two categories which have different clinical implications. The first one, unidirectional block and re-entry in the A V junction is responsible for the production of reciprocal beating (return extrasystole) and other arrhythmias. The second one, local block and microre-entry may play an important role in the genesis of coupled premature systoles, ectopic tachycardias, and atrial or ventricular fibrillation.

Reciprocal rhythm the most likely example of re-entry within the A V junction has been known both clinically and experimentally from the beginning of this century[44,4] To explain this arrhythmia, functional dissociation in some portions of the A V conducting system was postulated by some investigators, while others considered the possibility of dual or multiple pathways.[46] Recently it has been experimentally demonstrated that inhomogeneity of conduction permitted a slow but successful transmission of an impulse to the ventricles preferentially through the left side of the A V node and the same impulse turned and re-entered the right

side of the A-V junction where forward conduction showed marked decrement and block. Thus, the pathway of re-entry has been finally plotted and the role of functional dissociation of the A-V junctional tissues in reciprocal rhythm established.[49]

On the other hand, physiological evidence for a dual A-V conducting system was previously reported by Moe and associates.[9] These authors suggested that one of the pathways having a longer refractory period could transmit an impulse more rapidly, while the other pathway showed shorter refractory period and slower conduction velocity. Hence, a premature beat may be transmitted slowly in the pathway which recovered earlier. The impulse could then re-enter the more rapidly conducting pathway in an opposite direction after expiration of its longer refractory period. However, neither a significant role of refractoriness nor a marked difference in the action potential duration between two parallel portions of tissue has been observed within the A-V node. Hence, reciprocal beating probably results from functional longitudinal dissociation of the A-V junctional tissues due to inhomogeneous conduction (or different degrees of decrement in different portions) and unidirectional block. Furthermore, repetitive reciprocation has often been suggested to explain some instances of supraventricular tachycardia.[61,62] Mendez and Moe[60] showed experimental records suggesting repetitive re-entry within the A-V junction of isolated rabbit hearts. However, the actual pathway of re-entry has not been plotted in the presence of tachycardia due to repetitive reciprocation.

Another mechanism of re-entry in the A-V junction may come into operation in the presence of Wolff-Parkinson-White (pre-excitation) syndrome. In this instance, an accessory (or anomalous) pathway bypasses some portion of the A-V junctional tissues[64,65] and often permits transmission of impulses exclusively in forward or retrograde direction. Thus, anatomical rather than physiological separation of two pathways can form a re-entry circuit. When conduction in either the normal A-V junctional or the accessory pathway becomes unidirectional, sustained re-entry movement (or a type of circus movement) could precipitate supraventricular tachycardia. However, experimental studies on this mechanism have been few[66] and are still required.

On the other hand, unidirectional block without re-entry, as evidenced by retrograde conduction of idioventricular beats to the atria in the presence of high-grade forward conduction block, presents another variety of A-V conduction disturbance. Various theories have been proposed to explain this phenomenon.[67] Some investigators deny the possibility of retrograde transmission through the region of forward block and postulate the formation of a new impulse in the A-V junction above the blocked area due to mechanical stimulation of automatic fibers by ventricular contraction.[68,69] Others support the concept of unidirectional block,[70,71] although direct experimental evidence for such block in the A-V node has long been lacking. A somewhat compromised view between these two theories invokes electrotonic spread of current, skipping over the blocked region to account for retrograde conduction.[72] Although studies utilizing microelectrode techniques have generally denied electrotonic type of transmission within the A-V node,[41] electrotonic current may at least modify action potential configuration in the presence of depressed A-V nodal conduction.[73] A possible example of unidirectional block with different degrees of decrement in forward versus retrograde directions, resulting in successful retrograde atrial excitation in the presence of persistent A-V (forward) conduction failure, has recently been observed[48] (Fig. 4). Clinical records showing the production at will of 1:1 retrograde conduction during artificial ventricular pacing with rates exceeding that of the S-A node have also been presented as evidence for unidirectional block.[41,74] One argument against retrograde conduction across the blocked region was based on clinical observations of a short retrograde conduction time (R-P interval) in the presence of idioventricular beats showing wide QRS complexes. This argument has now lost its significance since aberrant intraventricular conduction of A-V nodal escape beats has been successfully explained by diastolic depolarization in Purkinje

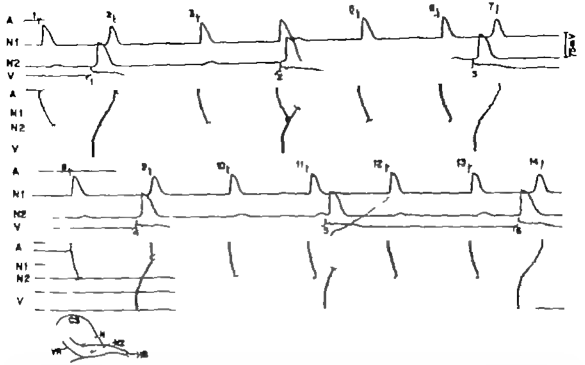

Fig 4 Experimental record showing unidirectional block in the A V junction. Abbreviations similar to those in Fig 3 Fibers *N1* and *N2* in the AN and the NH regions, respectively Atria and ventricles are driven at different rates as shown by stimulus artifacts. Action potentials of fiber *N1* (except those numbered *2 7 9* and *14*) follow atrial stimulation, which cause only a local response in fiber *N2* and fail to activate ventricles. Hence, complete forward (A V) conduction block is present. Ventricular stimulation always fully depolarizes fiber *N2* When the action potential of fiber *N2* occurs immediately following depolarization of fiber *N1* due to atrial stimulation (ventricular beats *2* and *5*) it causes a local response in fiber *N1* and fails to propagate further Thus, retrograde activation of fiber *N1* depends on the responsiveness of this region Otherwise the action potentials of fiber *N2* (numbered *1 3 4* and *6*) engender an action potential in fiber *N1* although with slower rate of depolarization, and successfully activate the atria (atrial beats *2 7* and *14*) except when the atria are refractory due to a driven beat (atrial beat *9*). Retrograde (V A) conduction is thus maintained in the presence of forward (A V) conduction block. Unidirectional block in this instance appears to result from dissimilar degrees of decrement in forward versus retrograde conduction, within the N region of the A V node.

fibers. Hence, judging from all the available data unidirectional conduction appears a most likely mechanism although final experimental proof is still required

A second and important category is local block with microre-entry This mechanism has long been invoked in the genesis of various ectopic rhythms.[78] The term microre-entry implies a small geometrical arrangement of the re-entry pathway as contrasted to the classical concept of circus movement in the explanation of atrial flutter This distinction must be clearly made Local block with microre-entry was first demonstrated by Schmitt and Erlanger[77] in 1928 utilizing isolated myocardial strips. In this instance asymmetrical depression of conductivity due to localized compression of the muscle initially engendered different conduction velocities in one direction vs. the other These alterations culminated in block of an impulse spreading into one region of the tissue and re-entry of the same impulse to this region from the distal end of a blocked area (Fig 5 left) Hence, this condition is analogous to the functional longitudinal dissociation observed in the A V node

On the other hand schematic anatomical structure, as shown in Fig 5 right, is frequently utilized in the explanation of the local re-entry movement. It will be readily understood that this model differs from the one just discussed (Fig 5 left) only by the anatomical instead of func

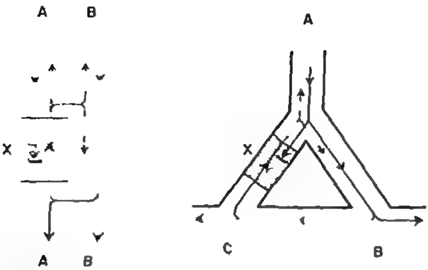

Fig 5 Schematic representation of re-entry movement. The left diagram correspond to functional longitudinal dissociation of cardiac tissue into two parallel portions. Unidirectional block is present at X. Re-excitation of the initially depolarized area is shown by dotted lines The right diagram illustrates anatomically separate pathway causing re-entry *AB* and *AC* could represent ramifications of a peripheral Purkinje fiber and *BC* ventricular myocardium. See text for discussion.

tional separation of two pathways conducting *forward and retrograde* respectively The mechanism which prevents forward transmission of an impulse, but permits subsequent retrograde conduction through the region X is most likely dissimilar degrees of decrement depending on the direction of transmission (unidirectional block) A longer duration of refractoriness in this region although less likely may not be ruled out as an alternative mechanism That such an anatomical arrangement of fibers can actually be found at junctions between peripheral branches of the Purkinje system and the ventricular myocardium has been pointed out by Hoffman.

Hoffman[3] has also suggested another possible mechanism of re-excitation in a similar model If forward conduction across the region X (Fig 5 right) is markedly slowed and retrograde transmission is blocked the peripheral tissue (BC) initially depolarized through the faster conducting pathway (AB) after the expiration of its refractory period may be discharged for a second time by the slowly spreading forward impulse through AC. Although this mechanism is somewhat different from the usual concept of re-entry unidirectional block again plays an important role. However the available data suggest *a more common occurrence of unidirec*tional block when an impulse proceeds from the Purkinje to ventricular fibers rather than in the opposite direction.[78] It has been shown that Purkinje-myocardial latency is always greater than myocardial-Purkinje latency and that conduction block due to high frequency of stimulation occurs earlier in Purkinje-myocardial direction.[78] Delay and failure of Purkinje papillary propagation with varying conduction ratios has also been observed during the early phase of spontaneous ventricular fibrillation[79] In these instances, the block is not due to refractoriness of either tissue.

Two explanations have been offered for the genesis of unidirectional block in the Purkinje ventricular junction (1) The supply of one terminal branch of Purkinje system to a greater number of ventricular fibers may result in summation or convergence of impulses when excitation spreads from ventricular to Purkinje fibers, while the opposite will hold in Purkinje-ventricular transmission (2) Certain factors (e.g cardiac glycosides) could decrease the resting potential and depress conduction in Purkinje fibers before any significant alterations of the ventricular

action potentials are produced.[39] Hence, some of the Purkinje fibers may fail to participate in ventricular excitation when the ventricular fibers still show normal excitability and conductivity.[40]

In all these models of re-entry, either within the A-V junction or at any other portions of the myocardium, re-excitation of some fibers may cause a coupled premature systole which obviously requires an initiating beat. When an appropriate electrophysiological condition is present, the previously generated premature systole may act as another initiating beat and a self-sustaining arrhythmia may ensue. Some of the clinical and experimental ectopic tachycardias may well be the result of this mechanism.

There is general agreement that two factors, i.e., a decreased conduction velocity and a shorter refractory period, favor the development of re-entry. One serious challenge to the theory of re-entry has been that unless an extremely slow conduction velocity is present, a long re-entry pathway must be postulated to explain rather long coupling intervals commonly seen in clinical arrhythmias. However, various experimental studies have revealed the possibility of conduction velocity as slow as 2 to 5 cm. per second in the A-V node or in certain areas of myocardium with depressed conductivity.[41] Hence, an adequate explanation has been given to this criticism. The actual size of a re-entry pathway, less than 2 mm., was observed in the A-V junction.[42] Although final proof of the re-entry movement causing atrial or ventricular premature systoles is still lacking, data supporting the existence of this mechanism are accumulating steadily.

Combined disturbances of impulse formation and conduction

Certain cardiac arrhythmias result from combined disturbances of impulse formation and conduction. Those most familiar to the clinician are parasystole and ectopic rhythms with exit block. Obviously, many varieties of clinical arrhythmias such as atrial tachycardia with block could also represent concomitant disturbances in both impulse formation and conduction. However, these arrhythmias actually result from separate electrophysiological events occurring at two different sites, e.g., ectopic impulse formation in the atria and conduction block in the A-V junction. On the other hand, the two mechanisms deserving more detailed discussion are produced by close interaction or association of these disturbances (impulse formation and conduction) in a localized region of the myocardium.

Parasystole. A parasystolic rhythm is characterized by the maintenance of regular impulse formation in a protected ectopic pacemaking area. Depolarization of the remainder of the heart by the dominant pacemaker usually has no effect on the parasystolic focus. Two theories have been proposed to explain the mechanism of protection. Scherf[43] postulates a high inherent frequency of firing (often 300 per minute or higher) at the site of impulse formation, which keeps the pacemaker refractory to the invading excitation front. According to this theory, certain degrees of exit block (or failure of propagation of impulses formed in the pacemaking focus) must be present in many clinical cases of parasystole, where the observed rate of ectopic discharge is much slower than 300 per minute.[43] However, frequent observations of constant, slow parasystolic rate (e.g., 50 per minute) over a long period in the same patient suggest that other mechanisms may be responsible.

The second theory involves so-called protection (or entrance) block surrounding an ectopic pacemaker.[43,44] This zone of protection block must have the characteristics of unidirectional block, since it prevents the entrance of the sinus or other impulses into the pacemaking region while permitting the exit of impulses from this area. However, concomitant presence of exit block has to be postulated in some instances, where an expected ectopic beat fails to appear despite its apparent timing outside the refractory period of the surrounding cardiac tissues. In such instances, the block is no longer unidirectional but affects conduction in both directions, although to a dissimilar extent.

It has been known that fibers possessing high degrees of automaticity, as those in the S-A node, generally show a lower level of resting potential (or maximal diastolic

potential), a smaller action potential amplitude, and a markedly slower rate of depolarization than other cardiac fibers. All these factors engender a slow conduction velocity and may even cause decremental conduction. A similar situation may be prevalent in other portions of the specialized conducting system when automaticity is enhanced and the membrane potential significantly reduced by diastolic depolarization.[44] Then it is quite possible that increased automaticity in a group of specialized fibers may create an ectopic pacemaker but at the same time may make propagation of impulses through this region more difficult. This mechanism may cause both entrance and exit block. This intriguing concept of automaticity explaining the mechanism of parasystole on one basis has recently been suggested by Hoffman.[3] Along with the demonstration of exit block from an A-V nodal pacemaker, this theory appears more attractive in explaining the mechanism of protection than the concept of a high inherent frequency.

However, a parasystolic focus with rapid impulse formation[41] is by no means ruled out. In such instances unidirectional block may play a greater role in causing exit block rather than in protecting the focus, and its distinction from the next category of arrhythmias may be difficult. Thus, Pick[41] has suggested that the mechanism of protection may not be the same in every instance of parasystole. Furthermore, occasional and transient development of local unidirectional block, which protects extrinsic discharge of a group of automatic fibers but permits exit of a generated impulse, may cause an apparently coupled premature systole[1] as mentioned earlier. So-called intermittent parasystole may actually represent an intermediate form between this hypothetical mechanism and true parasystole. More conclusive studies on the nature of protection of a parasystolic focus are definitely required.

Ectopic rhythms with exit block. The possible electrophysiological mechanism of exit block from an ectopic pacemaker has been discussed in the preceding section. In contrast to parasystolic rhythm, the

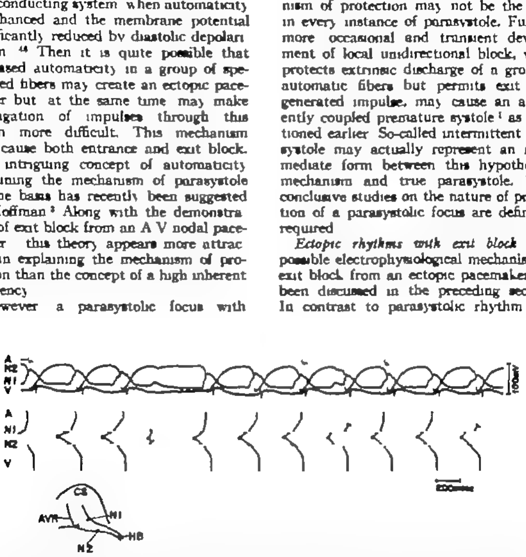

Fig. 6. Experimental record demonstrating exit block of A-V nodal impulses. Abbreviations similar to those in Fig. 3. Action potentials of fiber *N1* (N region) are recorded upright while those of fiber *N2* (NH region) with reversed polarity. X mark in the schematic map shows the earliest point of activation or the location of A-V nodal pacemaker. First three impulses cause successful activation of both atria and ventricles, although progressive slowing of the rate of depolarization with step-formation is seen especially in fiber *N1* action potentials. The fourth impulse engenders only local responses in both fibers and fails to excite the atria and ventricles (*forward and retrograde exit block*). Retrograde exit block alone is seen in the 8th and 11th beats. Note marked action potential step in both fibers *N1* and *N2* in the eighth beat. Typical Wenckebach periodicity is apparent in retrograde conduction to the atria, as frequently seen in clinical examples of such arrhythmia. The apparent foreshortening of the interval between the assumed timing of impulse formation (dot) and local response (beat 4) or step (beat 8) in fiber *N1* may be explained by (1) spontaneous premature firing of the automatic nodal center, (2) its premature discharge by local re-entry, (3) more than one conduction path to region *N1*, or (4) supernormal conduction. Presence of more than one functional pathway is perhaps most likely (cf. Fig. 3).

mechanism which allows regular impulse formation of an ectopic pacemaker is probably a higher frequency of discharge than that of the dominant pacemaker. Occasionally the presence of atrial or ventricular tachycardia with exit block is identified in clinical ECGs. However exit block is most commonly observed in accelerated A-V nodal rhythm due to digitalis excess.[16] Furthermore the rhythmicity of these ectopic pacemakers can sometimes be disturbed by a sinus impulse invading and discharging the pacemaking region. Exit block from an ectopic pacemaker frequently shows Wenckebach phenomenon. Hence the resultant arrhythmias are usually very complex.

In A-V nodal beating with exit block the cause of block is attributed to a small action potential amplitude with a slow rate of depolarization a mechanism favoring decremental conduction. Examples of exit block from a pacemaker located in a specific region of the A-V junction have been demonstrated recently utilizing microelectrode techniques[19] (Fig 6). Hence implications of ectopic rhythms with exit block in clinical ECGs now appear to stand on a firm electrophysiological basis.

Fibrillation

In spite of exhaustive studies, the mechanisms of atrial and ventricular fibrillation are still subject to great controversy. However it is readily understood that fibrillation may not represent an isolated electrophysiological entity but a result of various combinations of the individual mechanisms already discussed. Hence a brief review of the current theories rather than a detailed discussion of all the available data will be attempted. The mechanisms involved in both atrial and ventricular fibrillation appear quite similar although these two varieties stand in sharp contrast from each other as compared with their hemodynamic or clinical significance. The subject of atrial flutter will be included in this section as the theories and controversies on its mechanism have much in common with those on fibrillation.

It is rather widely accepted that the mechanisms which initiate the fibrillatory state and those sustaining this arrhythmia are not necessarily similar.[17] During established fibrillation the presence of numerous regions of microre-entries is now considered almost a certainty.[11, 7] Microre-entries, as a result of conduction disturbances are most likely the mechanism for the maintenance of fibrillation.

Historically several theories have been developed. They can be classified as (1) unifocal ectopic impulse formation (2) multifocal ectopic impulse formation and (3) re-entry. Combination of (1) or (2) and (3) is also possible. However some of these terms have been rather loosely defined by different investigators and thus caused further confusion and controversy. Hence clarification of these terms prior to the detailed discussion is warranted.

The term "unifocal impulse formation" implies impulse formation in a small localized area of myocardium other than S-A node. The mode of impulse formation can be any one of the several mechanisms i.e. automaticity oscillation afterpotentials, and local potential difference and the above term does not necessarily imply an increased diastolic depolarization in the focus. The same discussion applies to multifocal impulse formation. On the other hand re-entry usually implies a circus movement over a relatively long pathway involving a larger tissue mass although other investigators suggest microre-entry within a few cardiac fibers. Hence many inconsistencies and unnecessary controversies have filled the literature over the past 50 years. The role of a large circus movement now appears to be limited to certain types of atrial flutter[19] or sustained re-entry in the presence of pre-excitation syndrome while the concept of microre-entry has gained increasing support from recent electrophysiological studies.[26] Therefore the distinction between these two varieties of re-entry must be clearly made in any discussion of fibrillation.

Studies utilizing microelectrodes in the presence of established atrial or ventricular fibrillation have revealed that almost complete electrical disorganization of the respective chambers is present.[8] However some degree of synchrony may be observed between fibers separated by a distance less than 1 mm.[8] It is also abundantly clear that a shortened refractory period must necessarily be present for

disorganized fibers to undergo rapid repetitive discharge. This led Burn[80] to conclude that "fibrillation is caused by factors which throw fibers out of phase in the presence of decreased duration of refractory period."

The theory of unifocal impulse formation invokes a rapid firing of a pacemaker from a single ectopic focus. If this mechanism alone is operative, shortening of the action potential duration may be expected. However, disorganized cellular activities cannot be adequately explained. It has been argued that with a high frequency of stimulation, some fibers fail to respond to every impulse and islands of refractory tissue cause an irregular spread of excitation.[77] Indeed, this mode of initiation of asynchrony is quite possible. However, once irregular spread of excitation is invoked, it automatically implies local conduction disturbances, and the probability of microre-entry is inescapable. The strongest argument against the unifocal theory has been raised by experiments in which the fibrillating atria are cut into many smaller pieces, and the fibrillatory state is maintained in divided sections until a certain minimal mass is reached.[81] Although unifocal impulse formation may thus initiate fibrillation, other mechanisms appear more likely for its maintenance.

On the other hand, multifocal impulse formation could account for the fractionation of excitation, as different portions of the myocardium may respond to numerous, independently formed impulses from these foci. However, the experimental application of aconitine on a single localized area is sufficient to produce atrial or ventricular fibrillation. Hence simultaneous development of oscillatory potentials[77] in multiple foci neither are required nor can be invoked. Similar arguments may be applied to atrial fibrillation caused by electrical stimulation with or without vagal stimulation.[83,84] Another objection to the multifocal theory is based on the abrupt spontaneous termination of fibrillation. Simultaneous cessation of all impulse formation in numerous foci is unlikely.

The third theory, involving local conduction disturbances with possible microreentry, or combination of this mechanism with disturbances of impulse formation, appears to give the most plausible explanation for cellular disorganization. In both clinical and experimental fibrillation, two initiating mechanisms have been identified. The first (Type A)[77] is characterized by rapid onset of fibrillation with one or two premature systoles early in the repolarization phase of a previous ventricular (or atrial) excitation. Contrarily, Type B shows a gradual development of disorganization following a sustained period of tachycardia[78] (Fig. 7).

In Type A, a very early premature systole falling in the "vulnerable period"[77] produces varying degrees of incomplete depolarization in different fibers, due to variations of the duration of refractoriness.[7] Local conduction block is thus prevalent, and slow, irregular spread of excitation with multiple regions of microreentry causes asynchrony between fibers. The genesis of early premature systoles could be attributed to disturbances of either impulse formation or conduction. Shortening of the action potential duration with asynchronous repolarization of adjacent fibers appears as a rather common predisposing factor for this type of fibrillation. Furthermore, the role of acetylcholine or vagal stimulation in atrial fibrillation and that of digitalis or ischemia in ventricular fibrillation may be explained on this basis. In some instances, ventricular fibrillation may be initiated by a ventricular premature systole with a long coupling interval or even by an idioventricular escape beat. However, these initiating beats are usually followed by one or more subsequent beats with progressively shorter coupling intervals. These beats in turn produce a similar sequence of electrophysiological events as in the typical examples of Type A. It is possible that abnormal spread of excitation of an ectopic impulse may facilitate the production of very early premature systoles, especially in a more severely diseased or vulnerable heart. In these instances, generation of a local potential difference due to inhomogeneity of the myocardium with asynchronous repolarization may well be the cause of a very short coupling interval.

In Type B, gradual transition from

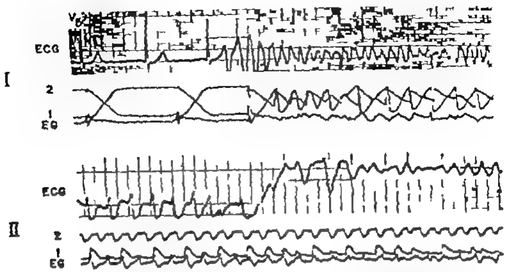

Fig. 7. Panel I shows Type A initiation of ventricular fibrillation. A ventricular premature systole with a short coupling interval causes rapid disorganization of the ventricles in both clinical ECG (top) and experimental animal (bottom). In the experimental record, upright (1) and inverted (2) action potentials of two adjacent ventricular fibers are shown together with ventricular electrogram (EG). Panel II shows Type B of the onset of fibrillation. Sustained period of ventricular tachycardia is followed by gradual transition into fibrillation in clinical and experimental records. Detailed discussion in text.

tachycardia to fibrillation is usually preceded by (1) the development of prominent electrical alternation of some fibers accompanied by further decrease in the rate of depolarization in the majority of fibers,[73, 88] and (2) fluctuations of the relative timing of depolarization in individual fibers[73] (Fig. 7). The first observation suggests the development of local block and the second implies variation in the spread of excitation from beat to beat. High frequency of stimulation apparently exaggerates inhomogeneity of the myocardium which causes a nonuniform shortening of the refractory period and produces a local block. In keeping with these concepts local block has been demonstrated at the Purkinje-ventricular muscle junction in the presence of rapid stimulation.[19] Sano and Scher[94] found an extreme tachysystole (up to 3,000 per minute) at the site of electrical stimulation during the onset of atrial fibrillation. Although this was considered as an evidence of unifocal activity, it could not be determined whether this tachysystole was due to increased automaticity or due to microre-entries.[89]

Attempts have been made to correlate the genesis of fibrillation with transmembrane flux of various ions, especially of potassium, sodium, calcium, and chloride.[95, 96] Since their effects may be considered rather indirect in terms of electrophysiology, detailed considerations on this subject will not be presented.

Finally, atrial flutter appears to result from two different mechanisms, at least in the experimental model. The first one, usually ascribed to unifocal impulse formation, is observed following topical application of aconitine.[91] The second variety, seen with electrical stimulation in the presence of an artificial obstacle in the path of conduction, appears to be an example of a circus movement.[98] This apparently continuous movement of the excitation front along a large circuitous pathway may very well be a type of reentry with unidirectional block. Possible transition between unifocal impulse formation and circus movement has been discussed by Smith and colleagues[99] in the genesis of ventricular flutter. Nevertheless, a generalized slowing of conduction velocity may play an important role in the production of atrial flutter, either due to a unifocal activity or a circus movement. Whether a difference in conduction velocity or frequency of firing alone could satisfactorily explain the clinical varieties

of atrial tachycardia and flutter in the presence of unifocal impulse formation awaits further identification

Summary

Current concepts on the electrophysiological basis of cardiac arrhythmias have been reviewed by incorporating some of the latest information with the time honored theories and observations of previous investigators. It is inevitably and hopefully anticipated that confirmation or denial of the various hypotheses will soon result in further identification of these concepts.

Addendum

After this paper was submitted for publication more detailed experimental work has been published on conduction disturbances due to diastolic depolarization in Purkinje fibers. For discussions of decremental conduction, re-entry, and supernormal conduction in Purkinje fibers, refer to Singer, D. H., Lazzara, R., and Hoffman, B. F.: Interrelationships between automaticity and conduction in Purkinje fibers, Circulation Res. 21:537, 1967.

REFERENCES

1. Hoffman, B. F.: Physiologic basis of disturbances of cardiac rhythm and conduction, Progr. Cardiovas. Dis. 2:319, 1959.
2. Hoffman, B. F., and Cranefield, P. F.: The physiological basis of cardiac arrhythmias, Am. J. Med. 37:670, 1964.
3. Hoffman, B. F.: The electrophysiology of heart muscle and the genesis of arrhythmias, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, New York, 1966, Grune & Stratton, Inc., p. 27.
4. Hoffman, B. F., and Cranefield, P. F.: Electrophysiology of the heart, New York, 1960, McGraw-Hill Book Company, Inc.
5. Parronnet, A. E., and Miller, R.: The influence of ventricular systole upon auricular rhythm in complete and incomplete heart block, Am. Heart J. 27:676, 1944.
6. James, T. N.: Anatomy of the human sinus node, Anat. Rec. 141:109, 1961.
7. Dudel, J., and Trautwein, W.: Das Aktionspotential und Mechanogram des Herzmuskels unter dem Einfluss der Dehnung, Cardiologia 25:344, 1954.
8. James, T. N., and Nadeau, R. A.: Sinus bradycardia during injections directly into the sinus node artery, Am. J. Physiol. 204:9, 1963.
9. James, T. N., and Nadeau, R. A.: Relation of retrograde pressure in the sinus node artery to sinus tachycardia from stellate stimulation, J. Lab. & Clin. Med. 62:777, 1963.
10. Paes de Carvalho, A., de Mello, W. C., and Hoffman, B. F.: Electrophysiological evidence for specialized fiber types in rabbit atrium, Am. J. Physiol. 196:483, 1959.
11. Paes de Carvalho, A.: Cellular electrophysiology of the atrial specialized tissues, in Paes de Carvalho, A., de Mello, W. C., and Hoffman, B. F., editors: The specialized tissues of the heart, Amsterdam, 1962, Elsevier Press, Inc., p. 115.
12. Ueda, H., Sugimoto, T., Murao, S., Kato, K., Harumi, K., Mashima, S., Kuroiwa, A., Sato, C., and Shimomura, K.: Arrhythmias produced by cardiac nervous stimulation, Jap. Heart J. 4:356, 1963.
13. Watanabe, Y., and Dreifus, L. S.: The site of impulse formation within the atrioventricular junction, Physiologist 9:315, 1966.
14. Hoffman, B. F., and Suckling, E. E.: Effect of several cations on transmembrane potentials of cardiac muscle, Am. J. Physiol. 186:317, 1956.
15. Coraboeuf, E., De Loze, C., and Boistel, J.: Action de la digitale sur les potentials de membrane et d'action du tissu conducteur du coeur de chien étudiée à l'aide de microélectrodes intracellulaires, Compt. rend. Soc. biol. 14:1169, 1953.
16. Dudel, J., and Trautwein, W.: Elektrophysiologische Messungen zur Strophanthinwirkung am Herzmuskel, Arch. exper. Path. u. Pharmakol. 232:393, 1958.
17. Vassalle, M., Karis, J., and Hoffman, B. F.: Toxic effects of ouabain on Purkinje fibers and ventricular muscle fibers, Am. J. Physiol. 203:433, 1962.
18. Moore, E. N., Morse, H. T., and Price, H. L.: Cardiac arrhythmias produced by catecholamines in anesthetized dogs, Circulation Res. 15:77, 1964.
19. Trautwein, W., and Kassebaum, D. G.: On the mechanism of spontaneous impulse generation in the pacemaker of the heart, J. Gen. Physiol. 45:317, 1961.
20. Vassalle, M.: Cardiac pacemaker potentials at different extra- and intracellular K concentrations, Am. J. Physiol. 208:770, 1965.
21. Surawicz, B., and Gettes, L. S.: Two mechanisms of cardiac arrest produced by potassium, Circulation Res. 12:415, 1963.
22. Surawicz, B., Chlebus, H., Reeves, J. T., and Gettes, L. S.: Increase of ventricular excitability threshold by hyperpotassemia, J.A.M.A. 191:1049, 1965.
23. Vassalle, M., Greenspan, K., and Hoffman, B. F.: An analysis of arrhythmias induced by ouabain in intact dogs, Circulation Res. 13:132, 1963.
24. Hellerstein, H. K., and Turell, D. J.: The mode of death in coronary artery disease. An electrocardiographic and clinicopathological correlation, in Surawicz, B., and Pellegrino, E. D., editors: Sudden cardiac death, New York, 1964, Grune & Stratton, Inc., p. 17.
25. Rothberger, C. J., and Sachs, A.: Rhythmicity

and utomatism in the mammalian left auricle, Quart. J Exper Ph siol. 29:69 1939
26. Muller P Ca and K free solution and pacemaker activity i mammalia myocardium, Helvet. physiol. acta 23:C38 1965
27 Da ies, F Davies, R. E., Francis, E. T B and Whittam, R. The sodium and potass m content of cardiac and other tissues of the ox, J Physiol. 118:276 1952.
28. Mazel, P and Holland W C. Acetylcholine and electrolyte metabolism in the various chambers of the frog and turtle heart, Circulation Res. 6:684 1958.
29 Bozler E The initiation of impulses in cardiac muscle Am. J Physiol. 138:273 1943
30. West T C. Effects of chronotropic influences on subthreshold oscillations in the sino-atrial node, in Paes de Carvalho, A de Mello, W C., and Hoffman, B. F ed tors The specialized tissues of the heart, Amsterdam, 1962, Elsevier Press, Inc., p. 81
31 Matsuda, K., Hoshi, T and Kameyama, S. Effects of aconitine on the cardiac membrane potential of the dog Jap. J Physiol. 9:419 1959
32. Sleator W and de Gubareff T Transmembrane action potentials nd contraction of h man trial muscle, Am. J Physiol. 206:1000 1964.
33. Brooks, C McC. Hoffman, B. F Suckling E. E., and Orias, O The excitability of the heart, New York, 1955 Grune & Stratton, Inc.
34. Scherf, D and Schott, A Extrasystoles and allied arrhythmias, London, 1953 William Heinemann, Ltd
35 Watanabe, Y and Dreifus, L. S Genesis of ventricular arrhythmias, in Brest, A N and Moyer J H editors Cardiovascular drug therapy New York, 1965 Grune & Stratton, Inc., p. 442.
36. M tsumura, M and Takaori, S The effect of drugs on the cardiac membrane potentials in the rabbit. II Auricular muscle fibers and the sinoatrial node, Jap J Pharmacol. 8 143, 1959
37 W tanabe Y and Dreifus, L. S. Electrophysiologic effects of digitalis on A V transmission, Am J Physiol. 211 1461 1966.
38. Hoffman, B. F Moore, E. N Stuckey J H and Cranefield, P F Functional properties of the atrioventricular conduction system. Circulation Res. 13:308 1963
39 Moore, E. N. Microelectrode studies on concealment of m ltiple premature trial responses, Circulation Res. 18:660, 1966
40. W tanabe, Y and Dreifus, L. S Inhomogeneous conduction in the A V node. A model for re-entry Am Hear J 70:505 1965
41 Hoffman, B. F., Paes de Carvalho, A., de Mello, W C and Cranefield, P F Electrical activity of single fibers of the atrioventricular node, Circulation Res. 11 1959
42. Cranefield, P F Hoffman, B F and Paes de Carvalho, A. The effect of acetylcholine on single fibers of the A V ode, Circulation Res. :19 1959
43 W tanabe, Y and Dreifus, L. S. Interactions of quinidine and potassium on atrioventricular transmission Circulation Res. 20:434 1967
44. M tsuda, K. Hoshi, T and Kameyama, S. Action of acetylcholine and adrenaline upon the membrane potential of the atrioventricular node (Tawara) Tohoku J Exper Med. 68 16, 1958.
45 Van Dam, R T Moore, E. N and Hoffman, B. F Initiation and conduction of impulses in partially depolarized cardiac fibers, Am J Physiol 204 1133 1963.
46. Weidmann, S. Elektrophysiologie der Herzmuskelfaser Bern, 1956, Hans Huber
47 Weidmann, S Effects of calcium and local anesthetics on electrical properties of Purkinje fibers, J Physiol 129:568, 1953
48. Langendorf R., Pick, A., and Winternitz, M. Mechanisms of intermittent ventricular bigeminy I Appearance of ectopic beats dependent upon length of the ventricular cycle, the rule of bigeminy Circulation 11:422, 1955.
49 Watanabe, Y and Dreifus, L. S Second degree atrioventricular block, Cardiovas. Res. 1:150, 1967
50. Watanabe, Y and Dreifus, L. S. Mechanisms of supernormal A V conduction, Fed. Proc. 25:635 1966.
51 Truex, R. C Anatomical considerations of the human atrioventricular junction, in Dreifus, L S. and Likoff W editors Mechanisms and therapy of cardiac arrhythmias, New York, 1966 Grune & Stratton Inc., p. 333
52. Hoffman, B F Cranefield, P F and Stuckey J H. Concealed conduction, Circulation Res. 9 194, 1961
53 Moe, G. K., Abildskov J A and Mendez, C. An experimental stud of concealed conduction, Am. Heart J 6 :338, 1964.
54 Langendorf R., Pick, A., Edelist, A., and Katz, L. N Experimental demonstration of concealed A V conduction in the human heart, Circulation 32:386, 1965.
55 Moore, E N Microelectrode studies on retrograde concealment of multiple premature ventricular responses, Circula ion Res. 20:88, 1967
56 Mines, G. R On d namic equilibrium in the heart, J Ph siol 46:349 1913
57 White, P D A study of trioventricular rhythm following auricular flutter Arch. I t. Med. 16:517 1915
58. Scherf D and Shookhoff C Experimentelle U tersuch ngen über die Umkehr Extrasystole Wien Arch. inn Med 12:501 1926.
59 Moe, G. K Preston, J B and Burlington, H Physiologic evidence for dual A V transmission stem, Circulation Res. 4:357 1956
60. Kist n, A D Mechanisms determining reciprocal rh thm initiated by ventricular extrasy toles. M ltiple pathway of conduction, Am J Cardiol. 3:365 1959
61 Barker P S., Wilson, F N and Johnston

F. D.: The mechanism of auricular paroxysmal tachycardia, Am. Heart J. 26:435, 1943.

62. Pick, A., and Langendorf, R.: A case of reciprocal beating with evidence of repetitive and blocked reentry of the cardiac impulse, Am. Heart J. 40:13, 1950.
63. Mendez, C., and Moe, G. K.: Demonstration of a dual A-V nodal conduction system in the isolated rabbit heart, Circulation Res. 19:378, 1966.
64. Wood, F. C., Wolferth, C. C., and Geckeler, G. D.: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short P-R interval and prolonged QRS complex, Am. Heart J. 25:454, 1943.
65. Lev, M., Sodi-Pallares, D., and Friedland, C.: A histopathologic study of the atrioventricular communications in a case of WPW with incomplete left bundle branch block, Am. Heart J. 66:399, 1963.
66. Butterworth, J. S., and Poindexter, C. A.: Short PR interval associated with a prolonged QRS complex. A clinical and experimental study, Arch. Int. Med. 69:437, 1942.
67. Scherf, D., and Cohen, J.: The atrioventricular node and selected cardiac arrhythmias, New York, 1964, Grune & Stratton, Inc.
68. Cullis, W. C., and Dixon, W. E.: Excitation and section of the auriculoventricular bundle, J. Physiol. 42:156, 1911.
69. Cohn, A. E., and Fraser, F. R.: The occurrence of auricular contractions in a case of incomplete and complete heart block due to stimuli received from the contracting ventricles, Heart 5:141, 1913.
70. Wolferth, C. C., and McMillan, T. M.: Observations on the mechanism of relatively short intervals in ventriculo-auricular and auriculo-ventricular sequential beats during high grade heart-block, Am. Heart J. 4:521, 1929.
71. Wintermitz, M., and Langendorf, R.: Auriculoventricular block with ventriculo-auricular response, Am. Heart J. 27:301, 1944.
72. Scherf, D.: Retrograde conduction in complete heart block, Dis. Chest 35:320, 1959.
73. Mendez, C., and Moe, G. K.: Some characteristics of transmembrane potentials of A-V nodal cells during propagation of premature beats, Circulation Res. 19:993, 1966.
74. Gobbay, E. R., and Mora, C. A.: Retrograde conduction and isorhythmic dissociation in heart block, Am. Heart J. 68:166, 1964.
75. MacWilliam, J. A.: Fibrillar contraction of the heart, J. Physiol. 8:296, 1887.
76. Lewis, T.: Mechanism and graphic registration of heart beat, London, 1925, Shaw and Sons, Ltd.
77. Schmitt, F. O., and Erlanger, J.: Directional differences in the conduction of impulse through heart muscle and their possible relation to extrasystolic and fibrillatory contractions, Am. J. Physiol. 87:326, 1928.
78. Alanis, J., Benitez, D., and Pilar, G.: A functional discontinuity between the Purkinje and ventricular muscle cells, Acta physiol. latinoamer. 11:171, 1961.
79. Watanabe, Y., and Dreifus, L. S.: Mechanisms of ventricular fibrillation, Jap. Heart J. 7:110, 1966.
80. Moe, G. K., and Mendez, R.: The action of several cardiac glycosides on conduction velocity and ventricular excitability in the dog heart, Circulation 4:729, 1951.
81. Scherf, D.: Zur Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, Ztschr. ges. exper. Med. 51:816, 1926.
82. Scherf, D., and Bornemann, C.: Parasystole with a rapid ventricular center, Am. Heart J. 62:320, 1961.
83. Kaufmann, R., and Rothberger, C. J.: Beitrag zur Kenntnis der Entstehungsweise der extrasystolischen Allorhythmien, Ztschr. ges. exper. Med. 5:349, 1917.
84. Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias, Philadelphia, 1956, Lea & Febiger Publishers.
85. Pick, A.: Parasystole, Circulation 8:243, 1953.
86. Dreifus, L. S., Katz, M., Watanabe, Y., and Likoff, W.: Clinical significance of disorders of impulse formation and conduction in the atrioventricular junction, Am. J. Cardiol. 11:384, 1963.
87. Moe, G. K., and Abildskov, J. A.: Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge, Am. Heart J. 58:59, 1959.
88. Sano, T., Tsuchihashi, H., and Shimamoto, T.: Ventricular fibrillation studied by the microelectrode method, Circulation Res. 6:41, 1958.
89. Moe, G. K., Rheinboldt, W. C., and Abildskov, J. A.: A computer model of atrial fibrillation, Am. Heart J. 67:200, 1964.
90. Rosenblueth, A., and Garcia Ramos, J.: Studies on flutter and fibrillation, Am. Heart J. 33:677, 1947.
91. Hogancamp, C. E., Kardesch, M., Danforth, W. H., and Bing, R. J.: Transmembrane electrical potentials in ventricular tachycardia and fibrillation, Am. Heart J. 57:214, 1959.
92. Burn, J. H.: The cause of fibrillation, Canad. M. A. J. 84:625, 1961.
93. Scherf, D.: The mechanism of flutter and fibrillation, Am. Heart J. 71:273, 1966.
94. West, T. C., and Landa, J. F.: Minimal mass required for induction of a sustained arrhythmia in isolated atrial segments, Am. J. Physiol. 202:232, 1962.
95. Nahum, L. H., and Hoff, H. E.: Production of auricular fibrillation by application of acetyl-β-methylcholine to localized regions on the auricular surface, Am. J. Physiol. 129:428, 1940.
96. Burn, J. H.: Ion movement and cardiac fibrillation, Proc. Roy. Soc. Med. London 50:725, 1957.
97. Wiggers, C. J., and Wegria, R.: Ventricular fibrillation due to single localized induction and condenser shocks applied during the vulnerable phase of ventricular systole, Am. J. Physiol. 128:500, 1940.
98. Sano, T., and Scher, A. M.: Multiple recording during electrically induced atrial fibrillation, Circulation Res. 14:117, 1964.

99. Sano, T. Recent advances in clarifying the genesis of cardiac fibrillation, Jap. Heart J. 6:387, 1965.
100. Grumbach, L., Howard, J. W., and Merrill, V. I. Factors related to the initiation of ventricular fibrillation in the isolated heart. Effect of calcium and potassium, Circulation Res. 2:452, 1954.
101. Holland, W. C. Potassium exchange in atrial fibrillation, Am. J. Physiol. 190:63, 1957.
102. Klein, R. L., and Holland, W. C. Na^{24} and K^{42} exchange in atrial fibrillation, Am. J. Physiol. 193:239, 1958.
103. Holland, W. C., and Sekul, A. A. Role of anions in the fibrillatory process, Am. J. Physiol. 198:841, 1960.
104. Scherf, D. Studies on auricular tachycardia caused by aconitine administration, Proc. Soc. Exper. Biol. & Med. 64:233, 1947.
105. Smirk, F. H., Nolla-Panades, J., and Wallis, T. Experimental ventricular flutter and ventricular paroxysmal tachycardia, Am. J. Cardiol. 14:79, 1964.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff Alan F Lyon and Julian Frieden

Surgical treatment of valvular heart disease

Part II. Criteria for operability in rheumatic heart disease

AORTIC VALVE LESIONS

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In contrast to the patient with mitral valve disease the individual with an aortic valve lesion has a potentially lethal problem of which he and his physician may be relatively unaware This is especially true of aortic stenosis. The left ventricle is able to compensate for an obstructive or insufficient, aortic valve for many years before symptoms occur and the only distinctive finding may be the murmur Once symptoms occur however progressive deterioration is inevitable and once cardiac failure ensues, the outlook becomes particularly grim A decision regarding surgical intervention is somewhat more difficult in these patients than in those with mitral valve disease Surgery almost inevitably entails valve replacement of some type and the follow up of various types of replacement is too short to justify a too enthusiastic approach to early surgery On the other hand valve replacement in a patient whose left ventricle is already severely damaged by years of stress cannot be expected to restore normal left ventricular function. In addition such patients are much more liable to lethal arrhythmias and conduction disturbances even though successful valve replacement is accomplished Finally such patients are on the average in an older age group when they come to surgery and coronary artery disease tends to be more of a complicating factor than in those patients with mitral valve disease.

It is now recognized that in any group of adult patients with isolated aortic stenosis, a large percentage of such cases will be of congenital etiology while those patients with combined aortic stenosis and insufficiency or those with multivalvular disease are more likely to be of rheumatic origin Furthermore there are many cases of isolated aortic insufficiency which are of nonrheumatic origin. Nevertheless since the surgical approach is generally the same all cases of aortic valve disease in the adult will be included in this discussion

Clinical appraisal

Symptoms The pathophysiology of aortic valve disease is such that the left ventricle is faced with a systolic overload (aortic stenosis) or a combined systolic-diastolic overload (aortic insufficiency or combined stenosis and insufficiency) As noted before the left ventricle is able to withstand this stress for many years before significant symptoms occur Indeed hemodynamic studies may show a considerably elevated left ventricular end-diastolic pressure in the

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absence of any subjective symptoms. Even in tight aortic stenosis or severe aortic insufficiency there is undoubtedly a long stable period of virtual absence of symptoms while the left ventricle continues to be subject to tremendous stress.

The earliest complaints are usually increased fatigability, dyspnea upon exertion, and vague dizziness with effort. Even with a strict medical regimen these symptoms tend to be progressive and eventually lead to one or more of a triad of ominous symptomatology, namely, (1) effort syncope, (2) angina pectoris, or (3) left ventricular failure. The onset of any of this triad of symptomatology, particularly cardiac failure, carries with it an average remaining life span of 2 to 4 years. Sudden death, which may occur in previously asymptomatic patients, is much more prominent after any of this triad of symptomatology occurs, and there is no way to predict it.

Physical findings

The auscultatory findings are often the first clue to the presence of aortic valve disease but may be of little help in judging its severity. Patients with aortic stenosis present with a crescendo-decrescendo systolic murmur usually maximal in the aortic area and radiating to the neck, but often well heard at the apex. The second sound is usually single or paradoxically split and the aortic component may be diminished in intensity. The presence of a fourth heart sound indicates a more severe lesion. Aortic insufficiency is associated with a decrescendo high frequency diastolic murmur beginning with the second sound and usually maximal at the left sternal border but also often well heard at the apex. Either lesion may be associated with diastolic activity at the apex which is easily mistaken for mitral stenosis. In the absence of an opening snap the diagnosis of mitral stenosis in such cases should be made with care.

The character of the carotid pulse[3] is most helpful in the diagnosis of aortic valve disease and to a certain degree in judging its severity. This is particularly true of aortic stenosis, where a small, slow rising, prolonged systolic wave usually indicates severe stenosis.

Electrocardiography and cardiac fluoroscopy

These clinical laboratory procedures are helpful in indicating the presence or absence of left ventricular enlargement in patients with aortic valve murmurs. Significant enlargement may occur in the absence of much symptomatology, but on the other hand, considerable symptomatology may be present without much demonstrated cardiac enlargement.

Hemodynamic appraisal

The use of hemodynamic studies to appraise the severity of an aortic valve lesion is considered unnecessary in many institutions. However, such studies are carried out in our institution as part of the evaluation of patients with aortic valve disease for the following reasons: (1) the fairly frequent finding of a significant aortic valve gradient or an elevated left ventricular end-diastolic pressure in patients without significant symptomatology or cardiac enlargement, (2) to evaluate the status of the coronary artery circulation, and (3) to exclude lesions of the mitral and tricuspid valves. Such studies are carried out as described in the previous article,[1] although frequently only a left heart and coronary study are done.

Type of surgery and risk involved

There is no longer any question that open heart technique is necessary for patients with aortic valve surgery. Unquestionably several patients were given a few years of added life following a closed aortic valvulotomy for aortic stenosis, but many were not improved and most eventually had recurrence of symptomatology. Nor has there been any successful closed approach to the valve which is markedly insufficient. Consequently, the surgery of aortic valve disease today entails an open procedure and replacement of the valve with a prosthetic device, with a homograft[4] or a heterograft[5] valve, or with some replacement tissue such as fascia lata. The operative risk is much the same with any of these techniques, varying from 6 to 18 per cent, depending upon the severity of the lesion and upon the presence or absence of other valve deformities. The long term fate of the patient undergoing any of these procedures

cannot yet be stated.[8] Definite complications, including ball degeneration, aortic insufficiency, and embolic phenomena occur in varying degree depending upon the type of surgery performed.

Selection of the patient for surgery. Although the ultimate fate of aortic valve replacement is not yet known, it can be stated with certainty that such procedures, when utilized in the patient who has reached one or more of the triad of symptomatology listed above, will give that patient a longer and more productive life than will medical therapy. Furthermore, this can be accomplished with an acceptable operative risk. The difficult decision to make is whether to subject the patient to aortic valve replacement before he has reached this stage of ominous symptomatology. However, the tendency is certainly toward a more early surgical approach. It is our feeling that patients with aortic valve murmurs who exhibit even minimal symptomatology, an abnormal carotid pulse contour, or any degree of cardiac enlargement should be considered for surgery. It is in this group of patients that hemodynamic appraisal is of the most value. The finding of a systolic aortic valve gradient greater than 50 mm. Hg, or the appreciation of significant aortic insufficiency by angiography, particularly if associated with a high left ventricular end-diastolic pressure would be considered indications for surgery. It is doubtful if there are any absolute contraindications to surgery other than some separate life-threatening disease or perhaps severe (triple vessel) coronary artery disease.

REFERENCES

1. Mitchell, A. M., Sackett, C. H., Hunzicker, W. J., and Levine, S. A.: The clinical features of aortic stenosis, Am. Heart J. 48:684, 1954.
2. Daoud, G., Reppert, E. H., and Butterworth, J. S.: Basal systolic murmurs and the carotid pulse in the diagnosis of calcareous aortic stenosis, Am. J. Med. 80:323, 1959.
3. Reppert, E. H.: Criteria for operability in rheumatic heart disease (Part I), Am. Heart J. In press.
4. Bristow, J. D., McCord, C. W., Starr, A., Ritzmann, L. W., and Griswold, H. E.: Clinical and hemodynamic results of aortic valvular replacement with a ball valve prosthesis, Circulation (Suppl. I) 29:36, 1964.
5. Ross, D.: Homograft replacement of the aortic valve, Brit. J. Surg. 54:842, 1967.
6. O'Brien, M. F., Clarebrough, J. K., McDonald, F. G., Hale, G. S., Bray, H. S., and Cade, J. F.: Heterograft aortic valve replacement: initial follow-up studies, Thorax 22:387, 1967.
7. Senning, Ake: Fascia lata replacement of aortic valves, J. Thoracic & Cardiovas. Surg. 54:465, 1967.
8. Duvoisin, G. E., Wallace, R. W., Ellis, F. H., Jr., Anderson, M. W., and McGoon, D. C.: Late results of cardiac valve replacement, Circulation (Suppl. II) 36:99, 1967.

Annotation

Cardiac tamponade as a late complication of open heart surgery

Although the insertion of prosthetic heart valves represents highly significant progress in cardiovascular surgery, complications continue to be recognized in the immediate and late postoperative periods. Problems encountered in the immediate postoperative period include cardiac arrhythmias, low cardiac output from multiple causes, pulmonary disturbances, and alterations in renal, hepatic, and neurological function. Systemic emboli, infection, prosthetic valvular regurgitation, anemia, and the postpericardiotomy syndrome may occur in the immediate as well as the late postoperative period. Arterial emboli continue to be the most frequent late complication associated with prosthetic valves, and anticoagulants seem warranted. The postpericardiotomy syndrome also occurs frequently, but it responds to therapy and doesn't alter convalescence. This report describes two patients with bloody pericardial effusions that occurred approximately 1 month after prosthetic valve replacement. The patients were anticoagulated and subsequently received salicylates for the postpericardiotomy syndrome when cardiac tamponade developed.

Patient M. B., a 10-year-old Negro girl, was admitted for mitral and tricuspid valve replacement. At age six she was found to have an apical pansystolic murmur which radiated into the back. Cardiac catheterization prior to operation revealed a large right atrium, right ventricular pressure of 70/26 mm. Hg, and marked mitral regurgitation demonstrated by cineangiography. On physical examination, the neck veins were not distended, but precordial heaves were present along the left sternal border and the anterior axillary line; a systolic thrill was palpable at the lower left sternal border. The second sound in the pulmonic area was closely split without respiratory variation, and a third sound was audible at the apex. A Grade IV/VI holosystolic murmur at the lower left sternal border radiated into the axilla and back with respiratory variation. The liver was 5 cm. below the right costal margin.

The patient's general deterioration and cardiac failure secondary to mitral and tricuspid regurgitation necessitated operation. The mitral and tricuspid valves were excised and each replaced with a 2M Starr-Edwards valve. A large pericardial window was created in closing the chest. Anticoagulation with warfarin sodium (Coumadin) was begun on the eighth postoperative day and the prothrombin time was maintained between 20 and 30 seconds with control of 12 seconds. The cardiac contours increased radiographically throughout the next seven days and then remained stable for the next five days. The cardiomegaly was attributed to moderate postoperative congestive failure. From the twelfth postoperative day, however, progressive enlargement of the cardiac silhouette occurred, and the chest film 29 days after operation was compatible with either severe cardiac dilatation or pericardial effusion.

Fever and cardiomegaly without apparent cause suggested the postpericardiotomy syndrome and salicylates were instituted (Fig. 1). In order to exclude malfunction of the mitral prosthesis, left ventricular cineangiography was performed which demonstrated slight regurgitation across the prosthesis. The prothrombin time increased from 28.2 seconds on the thirtieth postoperative day to 53 and 73 seconds over the subsequent two days. Prothrombin time decreased to 29 seconds after 20 mg. of vitamin K was given intravenously. The radiographic configuration of the heart and the patient's deteriorating condition prompted pericardiocentesis. The pericardial tap produced 500 ml. of nonclotting bloody fluid and the following day 400 ml. of similar fluid was removed. Subsequent attempts yielded no fluid and a venous angiogram did not demonstrate residual pericardial fluid. The patient clinically improved but suddenly died 13 days later. When the chest was opened for cardiac massage, approximately 50 ml. of serous pericardial fluid was found. At autopsy the prosthetic valves were intact without evidence of disruption or damage to the myocardium.

Patient N. P., a 45-year-old Caucasian woman, was admitted for surgical correction of mitral stenosis and regurgitation. The patient had rheumatic fever at age 12 and bacterial endocarditis at age 40. Subsequently, digitalis was required for management of cardiac failure and exercise tolerance became progressively diminished. On examination, the jugular venous pulse revealed an a wave, but the neck veins were not distended at 45 degrees. Precordial heaves were palpated at the left sternal edge and 2 cm. to the left of the midclavicular line. A pulmonic ejection click was present and the second sound was split normally with a palpable pulmonic component. A Grade IV/VI apical holosystolic

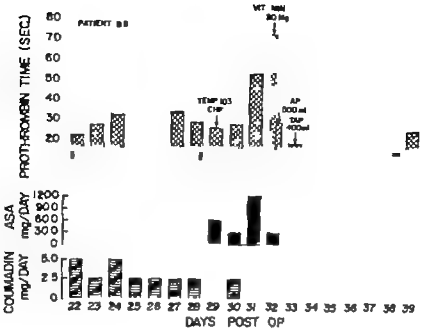

Fig. 1

murmur radiated to the back. A Grade I apical diastolic rumble and Grade I high pitched early diastolic murmur along the left sternal edge were also audible.

Cardiac catheterization disclosed pulmonary artery pressure of 64/28 mm. Hg, left ventricular end diastolic pressure 18 mm. Hg, and gradient of 12 mm. Hg across the mitral valve. Left ventricular angiography demonstrated mitral regurgitation. At operation severe mitral regurgitation was found and Starr-Edwards mitral prosthesis inserted. Anticoagulation with warfarin sodium was instituted five days after the operation, digitalis discontinued because of frequent premature ventricular contraction and the patient discharged one week later.

On the twenty-fifth postoperative day atrial fibrillation developed with a rate of 150 per minute. The patient became dyspneic and digitalis was restarted. One week later the rate had slowed to 110 per minute but symptoms remained unchanged. The patient was hospitalized and 35 days after her operation sinus rhythm was achieved with cardioversion. A pericardial friction rub was detected and review of postoperative chest films showed progressive cardiac enlargement. These findings suggested the postpericardiotomy syndrome and salicylates were given. The prothrombin time increased from 26 seconds on the thirty-sixth postoperative day to 58 seconds four days later. Two days after vitamin K was administered the prothrombin time was 19 seconds. A review of chest films during this time revealed a mediastinal collection of fluid and a pericardiocentesis was performed which yielded 300 ml. of bloody fluid with a hematocrit of 15 (patient hematocrit 37). On the following day 60 ml. of fluid with a hematocrit of 9 was removed. Subsequently the patient's dyspnea improved and her cardiac size decreased radiographically. She eventually was discharged and has continued to improve.

In each of the cases described, clinical deterioration occurred and the heart appeared to be larger radiographically with the prothrombin time in the therapeutic range. The administration of salicylates was followed by an increase in the prothrombin time in each instance. It cannot be stated that the effusions occurred because of the sudden prolongation of the prothrombin time. Since there had been progressive cardiomegaly one might speculate that an effusion had already accumulated. The blood in the effusion may well have been related to the increased bleeding tendency. The postpericardiotomy syndrome is a common postoperative complication in cardiac operation and certain aspects of this entity appeared in each case which prompted the administration of salicylates. Fever and cardiomegaly accompanied clinical deterioration in the first patient and a pericardial friction rub was heard in the second. Some have employed salicylates and continued anticoagulants without adverse effects, although high fever, severe chest pain, and loud pericardial friction rubs were present. The prolongation of the prothrombin time by salicylate is well known. Although the mechanism for salicylate induced hypoprothrombinemia has not been established it may be that salicylic acid depresses prothrombin synthesis by combining with the apoenzyme as does bishydroxycoumarin.

The possibility of a constricting pericardial effusion was initially considered unlikely in the first case because partial pericardiectomy had been performed at operation. In each patient the peri-

cardial fluid significantly impaired cardiac function, as demonstrated by improvement after aspiration. The reversibility of this complication emphasizes the importance of considering pericardial effusion and tamponade as the cause of cardiac enlargement and progressive heart failure after open heart operation. Particular caution should be observed when salicylates are administered under these circumstances with frequent monitoring of the prothrombin time and appropriate adjustment of the anticoagulant dosage.

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REFERENCES

1. Kloster, F. E., Bristow, J. D., and Griswold, H. E.: Medical problems in mitral and multiple valve replacement, Progr. Cardiovas. Dis. 7:504, 1965.
2. Duvoisin, G. E., Brandenburg, R. O., and McGoon, D. C.: Factors affecting thromboembolism associated with prosthetic heart valves, Circulation (Suppl. 1) 35:1-70, 1967.
3. Engle, M. A., and Ito, T.: The postpericardiotomy syndrome, Am. J. Cardiol. 7:73, 1961.
4. Urichio, J. F.: Postcommissurotomy (postpericardiotomy) syndrome, Am. J. Cardiol. 12:436, 1963.
5. McGuiness, J. B., and Taussig, H. B.: The postpericardiotomy syndrome, Circulation 26:500, 1962.
6. Williams, J. F., Jr., Morrow, A. G., and Braunwald, E.: The incidence and management of "medical" complications following cardiac operations, Circulation 32:608, 1965.
7. Quick, A. J.: Hemorrhagic diseases, Philadelphia, 1957, Lea & Febiger, Publishers, p. 120.

Beta-adrenergic receptor blockade in the diagnosis of pheochromocytoma

In a series of classical experiments performed early this century, Dale[1] showed that pretreatment with ergot not only abolished the usual pressor response to epinephrine but also reversed it, thus producing a depressor effect. Thus, he was the first to show that the catecholamines produce their effects by acting on at least two types of adrenergic receptors. Following a study of the relative potencies of a series of amines on a number of test organs, Ahlquist[2] proposed in 1948, that there are two types of adrenergic receptors; these he named the α- and β-receptors.

Blood vessels appear to possess both α- and β-receptors, stimulation of these results in vasoconstriction and vasodilation, respectively. α-Constrictor receptors are widely distributed, whereas β-dilator receptors are most numerous in blood vessels supplying skeletal muscle. Catecholamines produce their characteristic inotropic and chronotropic effects on the heart by an action on β-receptors. Epinephrine acts on both α- and β-receptors. By contrast, norepinephrine acts primarily on α-receptors but activates, in addition, cardiac β-receptors.

Following the administration of a β-receptor blocking agent such as propranolol, the pressor response to norepinephrine may be decreased while epinephrine, instead of producing a fall in systolic and a rise in diastolic blood pressure, now produces a pressor response similar to that produced by norepinephrine and accompanied by a reflex bradycardia.[3-5] The acute administration of β-receptor blocking agents to normal volunteers and to patients with essential hypertension does not produce an appreciable hypotensive response. However, after prolonged oral administration of these agents to patients with essential hypertension, a significant hypotensive action is apparent; the mechanism of this effect is still uncertain. The use of β-receptor blocking agents as hypotensive drugs has been reviewed by Prichard.

Pheochromocytomas produce markedly elevated circulating levels of norepinephrine and/or epinephrine. Dornhorst and Laurence[9] showed that Pronethalol, given in conjunction with an α-receptor blocking agent, produced useful control of the excessive cardiac stimulation resulting from the circulating catecholamines during the preoperative and operative management of such patients. These investigators warned that the use of a β-receptor blocking agent alone might lead to dangerous hypertensive crises in patients with pheochromocytoma. Paton[10] suggested that the blood pressure response to intravenously administered β-receptor blocking agents might be of value in the diagnosis of pheochromocytoma, particularly since such administration has little effect in normal subjects or patients with essential hypertension. He suggested that such tests might be most valuable in patients with histories of previous hypotensive paroxysmal attacks

a these patients would be the most likely t have predominantly epinephrine-secreting tumors. (I view of the effect of such agents on acutely administered catecholamines it might be anticipated that patients with predom nantly epinephrine-secreting tumors would exhibit greater pressor response than those with predominantly norepinephrine-secreting tumors.)

Prichard and Ross[11] subsequently reported that the oral dministration of propranolol produced a pressor response in 12 experiments on 5 patients with pheochromocytoma. However the nature of the response to propranolol aried and these investigators divided their patients into two groups on the basis of the esponses to propranolol. Patients in Group I showed marked rise in both systolic and diastolic blood pressures accompanied by brady cardia while those in Group II showed a slight rise in diast lic blood pressure bradycardia, nd a fall in systolic blood pressure The pressor response was also seen in the presence of phenoxybenzamine -receptor blocking agent to explain this finding, Prichard and Ross[11] suggested that propranolol had unmasked the incompleteness of the α-receptor blockad by phenoxybenzamine in these patients. This ould ppear to be valid explanation since only a small fraction of the total umber of adrener gic receptors present is req ired for a maximal response.[12] These workers also suggested that β-receptor blockade might reduce amine binding and thus increase the concentration of amine at the α-receptor this would seem to be an unlikely possibility since Thoenen and co-workers[13] have shown that there is no correlation between the intensity of α-adrenergic blocking action and the increase in th quantity of norepinephrine released on nerve stimu lation produced by a series of drugs Several α- and β-adrenergic blocking agents have the add tional ability of being able to inhibit the retention of catecholamines by sympathetically innervated or gans[14] and this property if operative in ma t the doses employed i these studies, would increase the local concentration of amine.

Prichard and Ross[11] reported that their patients Group I had predominantly norepinephrine-secreting tumors however no figures were given *in their paper to indicate the levels of circulating* amines. Engelman[8] by contrast reported seeing pressor responses to propranolol only when th tumor was epinephrine-producing

The findings of these workers indicat that further investigation is required to assess the diagnostic value of and the characteristics of those patients most likely to respond positively to β-adrenergic receptor blockade. I view of the accum lated knowledge about the effects of propranolol, certain modifications to the test proposed by Paton[10] would ppear warranted. The most important poi t to not is that intravenous propranolol can produce serious side effects and has on occasion proved f tal. Accordingly i tra enous propranolol should only be used diagnostically in unit equipped t provide immediate resuscitation while the initial dose given should be small (0.5 t 1.0 mg) nd repeated only hen the patient reactions have been noted.[1] Since Prichard and Ross howed that pressor response to propranolol occurred following oral administration this route would seem to be particularly worthy of study because of the reduced hazards involved. I view of the known ability of propranolol to precipitate cardiac f ilure and respiratory difficulty propranolol should not be used diagnostically in patients with impaired cardiac reserve or asthma. Phentolamine should be available for immediate intravenous administration in the event of a danger ous hypertensive crisis.

In conclusion propranolol (1) potentiates the pressor response to epinephrine but not to norepinephrine (2) has little effect on blood pressure when administered acutely to normal subjects and patients with essential hypertension and (3) produces a pressor response in t least certain patients with pheochromocytoma. Further investigation of its usef lness as diagnostic test for the presence of pheochromocytoma would ppear warranted

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REFERENCES

1 Dale, H. H O some physiological actions of ergot, J Physiol. 34 163 1906.
2. Dale, H H On the action of ergotoxine, with special reference to the existence of sympathetic vasodilators, J Physiol. 46:291 1913.
3 Ahlquist, R. P A study of the adrenotropic receptors Am. J Physiol. 153:586, 1948.
4 Paton, D M The catecholamines and their receptors, South African M J 39:656 1965
5. Shanks, R. G The effect of propranolol on the cardiovascular response t isoprenaline, adrenaline and noradrenaline in the anaesthetised dog, Brit. J Pharmacol. 26:322, 1966.
6. Harris, W S. Schoenfeld, C. D Brooks, R H. and Weissler A. M Effects of beta adrenergic blockade on the hemodynamic responses to epinephrine in man Am. J Cardiol. 17:484 1966.
7 Prichard B N C. Hypotension from beta adrenergic blocking drugs, Am. Heart J 69 716, 1965.
8. Prichard, B N C., and Gillam, P M S Propranolol in hypertension, Am J Cardiol. 18:387 1966.
9 Dornhorst, A. C., nd Laurence, D R. Use of Pronethalol i pheochroma tumors, Brit. M J 2 1250, 1963
10 Paton, D M Beta-receptor blockade in the diagnosis of phaeochromocytoma, Lancet 2 1123 1964
11. Prichard, B. N C., and Ross, E. J Use of propranolol i conjunction with lpha receptor blocking drugs in pheochrocytoma, Am J Cardiol. 18:394 1966.
12 Nickerson, M New developments i adrenergic blocking agents, Ann. New York Acad. Sc. 139:571 1967
13 Thoenen H Hürlima n, A., and Haefely W Wirkungen von phenoxybenzamin, phentolamin und azapetı auf adrenergische synapsen der katzenmilz, Hel et physiol. acta 22 148, 1964
14 Iversen, L. L. The uptake and storage of nor

adrenaline in sympathetic nerves, Cambridge 1967, Cambridge University Press.

15. Engelman, K. quoted by Wolfson, S., and Gorlin, R. Report on the discussion of Session V. Physiological and clinical aspects of beta adrenergic blockade, Ann. New York Acad. Sc. 139:1003, 1967.

16. Stephen, S. A. Unwanted effects of propranolol, Am. J. Cardiol. 18:463, 1966.

17. Goodwin, J. F. Discussion of side effects, Am. J. Cardiol. 18:468, 1966.

The use of furosemide in refractory heart failure

Increasing the dose of most of the currently available diuretics does not increase their effectiveness. Thus, increasing the dose of chlorothiazide from 1 to 2 Gm. per day or mercurial diuretics from 2 to 4 ml. seldom increases diuresis. Only recently since furosemide and ethacrynic acid have become available, has it been possible to mobilize large amounts of sodium in the presence of optimal doses of thiazides or organomercurials.

Although both drugs seemed to be equally potent, the lack of side effects following furosemide favored its use in a group of patients with severe congestive heart failure who had become refractory to both the thiazides and organomercurials. Complete clearing of edema was achieved in all patients in four to six days. In most patients, even though satisfactory diuresis followed the first injection, more profound diuresis followed subsequent injections. Roentgenography five days after the beginning of furosemide administration demonstrated disappearance of congestion and decrease in heart size in the majority of patients with acute pulmonary edema. The rapid clinical improvement in congestive heart failure was also reflected hemodynamically by the 25 per cent decrease in plasma volume, an 18 per cent increase in cardiac output, and a 22 per cent decrease in total peripheral resistance 2 hours following furosemide administration.

The onset of diuresis occurred within 1 to 2 minutes and the peak of diuretic action seemed to be at 25 to 30 minutes. There was a 1,389 per cent average increase in urinary output, 15 minutes following the injection of furosemide, a 472 per cent average increase in sodium excretion and a 147 per cent average increase in potassium excretion. Potassium excretion paralleled urinary output and the sodium-potassium excretion ratio was consistently increased.

The diuresis following furosemide seemed to depend on whether the patient had recently received other diuretics and on the amount of functioning renal tissue. A profound diuresis (more than 3 L. of urine in 2 hours) could follow relatively small doses (40 mg.) in a patient who had not received prior diuretic therapy and whose kidney function was not impaired. In those who were being treated with other diuretics 80 to 100 mg. of furosemide was needed to accomplish a similar diuretic response. These data suggest a starting dose of 40 mg. in patients who have not received prior diuretic therapy and whose renal function is good. In patients who have recently received diuretics, a starting dose of 60 to 80 mg. seems advisable. When there is impaired renal function the starting dose could be 100 mg. These doses can be increased every 30 to 60 minutes until diuresis occurs. Although doses of 1,000 mg. has been administered without toxic effects, more than 100 mg. is seldom needed to produce diuresis in the absence of renal impairment. It should be emphasized that a greater diuresis frequently followed the second and third injections even though a satisfactory diuresis followed the initial administration. In order to obtain the maximum therapeutic response, therefore, it seems advisable to continue furosemide therapy over a period of several days.

Toxic reactions or the development of tachyphylaxis were not observed either after the single administration of a large dose (1,000 mg.) or after repeated administrations of massive doses (4,100 mg. in 5 days). The only side effects which could be anticipated could be those due to excessive diuresis with a rapid depletion in plasma volume which occasionally followed relatively small doses of furosemide. In order to avoid this possibility, therefore, it is recommended that furosemide therapy be initiated in a dosage of 40 mg. If excessive diuresis does not occur the dose may be doubled and then tripled in a period of 24 to 48 hours. Once an effective dosage has been reached it may then be repeated daily or twice daily as the need arises.

It would seem, therefore, that furosemide is a significantly more potent diuretic than either organomercurials or thiazides—the drugs currently used to treat congestive heart failure. Equally important is the observation that the potency of furosemide may be further increased by increasing the dosage. The ability to tailor the dosage to the individual situation, the favorable sodium-potassium excretion ratio, the ability to exert its effect in the face of electrolyte imbalance and the lack of side effects favor the use of furosemide in the treatment of refractory pulmonary edema.

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REFERENCES

1. Moyer, J. H.: Human pharmacology of thiazide derivatives, J.A.M.A. 170:2048, 1959.
2. Ford, R. V., Moyer, J. H., and Spurr, C. L.: Clinical and laboratory observations on chlorothiazide (Diuril), Arch. Int. Med. 100:582, 1957.
3. Davidov, M., Kakaviatos, N., and Finnerty, F. A., Jr.: Intravenous administration of furosemide in heart failure, J.A.M.A. 200:824, 1967.
4. Davidov, M., Kakaviatos, N., and Finnerty, F. A., Jr.: Diuretic and antihypertensive properties of furosemide, J. New Drugs 6:123, 1966.
5. Hook, J. B., and Williamson, H. E.: Addition of the saluretic action of furosemide to the saluretic action of certain other agents, J. Pharmacol. & Exper. Therap. 148:88, 1965.

Unusual gastrointestinal reaction to bishydroxycoumarin (Dicumarol)

A 64-year-old Caucasian woman was admitted to Jewish Memorial Hospital on Oct. 4, 1965, because of sudden onset of severe chest pain. Electrocardiograms (ECG's) and laboratory studies confirmed the diagnosis of acute posterior wall myocardial infarction. Anticoagulant therapy was started with 75 mg. of heparin intramuscularly every 6 hours. Bishydroxycoumarin was also given at the same time. On Oct. 8, 1965, heparin was discontinued because an adequate prothrombin time within the therapeutic range had been obtained. Subsequently the dose of bishydroxycoumarin was adjusted between 50 and 75 mg. to keep the prothrombin time at an average of 20 seconds. At no time did the prothrombin time exceed 23 seconds.

On Oct. 23, 1965, the patient complained of abdominal cramps and diarrhea. All medications except bishydroxycoumarin were discontinued. Diarrhea persisted in spite of the administration of Kaopectate and Donnatal. Diarrhea became progressively worse and it was suspected that bishydroxycoumarin might be responsible. Therefore, on Nov. 10, 1965, bishydroxycoumarin was discontinued. Two days later the cramps and diarrhea had stopped completely. The patient was then given warfarin as an anticoagulant and experienced no further cramps or diarrhea.

On Jan. 17, 1967, while still on maintenance dose of warfarin, she had another myocardial infarct, this time anteroseptal. In view of the experience of the previous admission to the hospital, it was felt that bishydroxycoumarin should be tried again to be certain that it had really been the cause of the gastrointestinal symptoms. Therefore, on Jan. 18, 1967, bishydroxycoumarin was substituted for warfarin. On Jan. 20, 1967, the patient complained of abdominal cramps and diarrhea which got progressively worse until the drug was discontinued on Jan. 23, 1967. During this period of time the highest prothrombin time was 28 seconds, the average 21 seconds. On Jan. 25, 1967, cramps and diarrhea having stopped, the patient was again given warfarin and has been taking this drug since then without any side reactions. From January 18 to 23, the only medication other than anticoagulants was an evening dose of secobarbital which was continued throughout and obviously was not a factor in the production of gastrointestinal symptoms.

In this case severe gastrointestinal symptoms from the use of bishydroxycoumarin necessitated discontinuance of the drug. The reaction to bishydroxycoumarin did not occur with warfarin. This would appear to be a sensitivity reaction not related to toxic doses. The prothrombin time while receiving bishydroxycoumarin was at the low therapeutic rather than the high level. Whether this was a local gastrointestinal reaction or a central effect could not be determined in this patient.

The manufacturer has on record only four complaints since 1956 relating to gastrointestinal disturbances from bishydroxycoumarin in the form of various degrees of diarrhea. Considering the extensive use of this drug, diarrhea sufficient to cause discontinuance must be quite rare. However, diarrhea in a patient with a severe myocardial infarction can be a serious complication.

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Letters to the Editor

Atrial flutter

To the Editor:

In the annotations of the December 1967 issue of the Journal, there is a brief report by Lawrence Gould and Alan F. Lyon entitled "Conversion of atrial flutter to sinus rhythm after stimulation of carotid sinus." The report was presented to document the conversion of atrial flutter to sinus mechanism by carotid sinus stimulation. It fails to do this because the rhythm illustrated is not atrial flutter.

The top strip in the illustration shows a ventricular rate of close to 150 per minute. The base line is undulatory and suggests flutter waves with 2:1 block, alternate flutter waves being partly obscured by QRS complexes. What is actually occurring is the superimposition of an ectopic P wave on the downward limb of the preceding T wave. The rising deflection immediately before each QRS is related to the terminal portion of the T wave, and possibly a small upward deflection related to the ectopic P wave. The positive deflection between each QRS complex is the T wave which ends with the negative ectopic P wave. Inspection of the end portion of the second strip shows the onset of the ectopic arrhythmia. The first ectopic P wave is clearly shown. It precedes the fifth from last QRS complex on this strip. It occurs a good interval after the preceding T wave. There is a negligible positive deflection immediately in front of QRS. With the next beat however the ectopic P wave is again, as in the first strip, superimposed on the downward limb of the T wave. The terminal portion of the T wave now contributes to a rising deflection before QRS. The first two atrial beats are clearly seen here and indicate a rate of discharge of 150 per minute. There is a 1:1 A-V response. At the beginning of the second strip carotid sinus pressure is applied. After three normal QRS complexes there is a pause of ventricular activity for a little over 2 seconds. The two negative deflections, described as premature ventricular contractions in the legend, are actually ectopic atrial beats because (1) they are rather unusual in configuration for premature ventricular beats, (2) they are almost identical in appearance to the first ectopic P wave that occurs toward the end of this same strip, and (3) they fall perfectly in line with the preceding atrial beats at 150 per minute. In other words, at the arrow A-V block occurs before the ectopic focus is extinguished. In the third strip, 2:1 A-V block occurs for a few beats before the ectopic focus is extinguished and again, one can recognize clearly atrial activity at 150 per minute.

It is not possible to make a diagnosis of atrial flutter when the atrial rate is 150. This arrhythmia is best considered an example of atrial tachycardia. The reversion to normal sinus rhythm is of course the common response of atrial tachycardia to carotid sinus pressure.

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Reply

To the Editor:

In the 12-lead electrocardiogram obtained just prior to carotid sinus stimulation, two P waves preceded each QRS complex in Lead V_1. The typical saw tooth pattern of atrial flutter was observed in Leads II, III, and aVF. Thus, one is justified to conclude that this is a typical example of atrial flutter where the atrial rate is 300 per minute and the ventricular rate 150 per minute.

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Book reviews

THE ENIGMA OF CORONARY HEART DISEASE. By A. H. T Robb-Sm th M.A. M D Chicago, 1967 Year Book Medical Publishers, Inc. 150 pages. Price $6.50

This short monograph is clearly written nd summarizes very accurately and briefly the history and epidemiology of coronary heart disease. Dr Robb-Smith not only describes the major tudies reported in the medical literature but indicates in a provocative manner some of the difficulties in interpretation of the data and conclusions He frequently quotes statements of others to illustrate his points but they in turn reflect lack of concrete evidence for conclusions drawn. These are more opinions impressions and ideas of the investigators. The book further indicates the difficulties of epidemiologic investigations of such a complex problem as coronary disease especially the use of data collected in an i ter national cooperative study The bibliography is good and few tables of incidence are included. This is an interesting book. It should be of valu to those wh have an interest in epidemiologic studies of coronary heart disease.

ELECTROCARDIOGRAPHY IN THE DIAGNOSIS OF CON GENITAL HEART DISEASE. By G E Burch, M D and Nicholas P DePasquale, M D Philadelphia, 1967 Lea & Febiger Publishers 512 illustrations, 755 pages. Price $26 00

This is one of the most valuable books t be published in the last few years in cardiology It is one of those rare contributions that actually fulfill a true need.

As the authors point out, in the context of congenital heart disease, the electrocardiogram offers simple, inexpensive, and saf means of patient study and when evaluated in light of the bedside findings it usually narrows diagnostic possibilities t a minimum mber It is most potent tool when tilized with proper knowledge

The material in this book is presented in a well-organized and lucid manner The electrocardiographic and also vectorcardiographic findings of all of the common congenital heart disorders and most of the rare ones are presented systematically and in detail. I addition, helpful but succinct information for orientation purposes is given regarding pertinent anatomy and hemodynamics. The book abounds with clearly presented illustrations. Further there is a very complete bibliography and a helpf l ppendix. One of the outstanding features of the book is the provision of a detailed summary t the end of each chapter This is most rewarding to the reader since by reading the summary and glanc ing at the illustrations he is conveniently able to cement together and retain the many facts and concepts that are provided in the text. Further these summaries provide source for quick review and stimulation of recall t some time in the future.

The present reviewer can recommend this book without reservation. It is a must" for all physicians dealing with the evaluation of patients with congenital heart disease.

DIFFERENTIAL DIAGNOSIS OF CARDIOVASCULAR DISEASE BY X RAY By P H Meyers, M D M Roy M D and C. M Nice, M D New York 1966, Hoeber Medical Division, Harper & Row Publishers, Inc 187 pages. Price $10.50

In the preface, the authors, who are all radiologists state, "W have long felt the need for book designed to aid the practicing physician in the differential diagnosis of cardiovascular disease by providing him with a q ick, systematic, and comprehensive method of correlating the abnormalities visualized by oentgenographic tech niques with the results of clinical examination and labor tory tests. This volume will, we hope, answer that need

This reviewer feels the authors have fallen somewhat short of their mark. The book is presented largely in outline form and is supplemented with an atlas of 98 plates. Clinical and laboratory findings as well as the x-ray haracteristics are presented for th major cardiovascular disorders.

The information dealing with clinical and laboratory findings is frequently nsophisticated For the internist, and certainl for the cardi ologist, the areas concerned with radiologic findings offer largely material which is quite well known Further this reviewer has viewed much finer radiologic examples of various cardiovascular disorders than are provided in the tlas of this monograph.

I f ture editions, collaboration of the authors with well-informed clinical cardiologist would add immeasurably toward fulfilling the primary aim of this contribution. I its present form, this book would appear to be of valu only to the relatively uninitiated in radiologic cardiovascular diagnosis.

PROCEEDINGS OF THE THIRD WORLD CONGRESS OF ANESTHESIOLOGY Edited by P R. Bromage J E. Eckenhoff R. Frey T Cecil Gray M Digby Leigh Sir Robert R. Maci tosh L. E. Morris, J A. Neal, C. R. Ritsema van Eck, and M. Zindler Berlin, Heidelberg, New York, 1966 Springer Verlag, 173 pages.

This paper bound volume contains series of panel discussions, some of which are preceded by short formal presentations related to the subject matter Topics included are Catecholamines and their significance in anesthesia, Clinical use of halogenated agents, and "Anesthesia for cardiovascular surgery Some of the material

presented would be of interest to cardiologists. It is noteworthy that the participants are greatly concerned with the effects of drugs on the circulatory and respiratory systems, and they have presented their current experiences in a way that will serve as a useful guide to anyone contemplating anesthesia of patients with normal or disordered circulation. As might be expected from a spontaneous discussion program much verbiage of doubtful value to a reader remote from the program is included.

Books received

Determination and Diagnostic Significance of Lactate Dehydrogenase Isoenzymes. By H. A. Zondag. Assen, Netherlands, 1967, Van Gorcum & Company. 118 pages.

The Office Assistant in Medical Practice, ed. 3. By Portia M. Frederick and Mary E. Kinn. Philadelphia, 1967, W. B. Saunders Company. 461 pages. Price $7.50.

Psychoanalysis of Heart Attack. By Daniel E. Schneider. New York, 1967, Dial Press, Inc., 234 pages. Price $6.00.

Coronary Heart Disease in Kristiansund 1959 to 1961 (Norwegian Monographs on Medical Science). By R. Gundersen. Oslo, Norway, 1967, Universitetsforlaget, 178 pages. Price $7.50.

Modern Problems in Pediatrics. Vol. X, Cystic Fibrosis, Part I. Physiology and Pathophysiology of Serous Secretion, Clinical Investigations, and Therapy, by E. Rossi and E. Stoll. Proceedings of the 4th International Conference on Cystic Fibrosis of the Pancreas (Mucoviscidosis)—Geigy Symposium, Berne/Grindelwald, September 1966. Basel, 1967, S. Karger. 404 pages. Price $23.80.

Modern Treatment. Vol. 4, No. 6, November 1967. (1) Treatment of Obesity by Charles A. Hollenberg. (2) Treatment of Burns, by Charles L. Fox, Jr. New York, 1967, Hoeber Medical Division, Harper & Row, Publishers, Inc., 1,200 pages per year. Price $16.00 per year.

The Principles of Medical Computing. By Thomas R. Taylor. Philadelphia, 1967, F. A. Davis Company. 168 pages. Price $7.00.

Psychoanalysis of Heart Attack. By Daniel E. Schneider. New York, 1967, Dial Press, 234 pages. Price $6.00.

Sex and Your Heart. By Myron Brenton. New York, 1968, Coward McCann, Inc., 180 pages. Price $4.95.

Biology of the Howler Monkey. By M. R. Malinow. Basel, 1967, S. Karger. 232 pages. Price $12.50.

A Doctor Among the Addicts. By Nat Hentoff. Chicago, 1968, Rand McNally. 136 pages. Price $4.50.

Frontiers of Radiation Therapy and Oncology. Hyperbaric Oxygen and Radiation Therapy of Cancer. Vol. 1, edited by J. M. Vaeth. Basel, 1968, S. Karger. 200 pages. Price $12.50.

Grundprobleme der neuen Hämodynamik und therapeutische Konsequenzen. By P. Vogeler and J. C. Cordes. Leipzig, 1967, Veb Georg Thieme, 260 pages. Price $18.50.

Hamdard Medical Digest. Special Issue. Men of Science in Pakistan, Vol. X, July through November 1966, edited by Hakim Mohammed Said, 178 pages.

Announcements

A Five Day Congress in Cardiology will be held in Mexico Oct. 29 through Nov. 2, 1968, the week after the Olympic Games. The faculty will be composed of Abdo Bisteni, M.D., Mexico; P. G. F. Nixon, M.R.C.P., London; Joseph K. Perloff, M.D., Washington; and Jose Ponce de Leon, M.D., Mexico. The directors will be Demetrio Sodi-Pallares, M.D., Mexico and Henry J. L. Marriott, M.D., St. Petersburg.

For further details write to the Rogers Heart Foundation, 500 First Federal Building, St. Petersburg, Fla.

A Course in Interpretation of Complex Arrhythmias will be given at the Michael Reese Hospital and Medical Center by Alfred Pick, M.D., Richard Langendorf, M.D., and Louis N. Katz, M.D. This is an advanced course intended for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M. Tuition fee $150.00.

Further information and a copy of the lecture schedule may be obtained from the secretary, Cardiovascular Institute, Michael Reese Hospital and Medical Center, Chicago, Ill. 60616

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Editorial

Hemodynamics of hypertension

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Cardiovascular measurements in patients with hypertension have shown that in general the high arterial pressure is associated with a relatively normal cardiac output, and the systemic vascular resistance is considerably elevated. These changes persist on supine exercise, the cardiac output increasing in a relatively normal way unless there is serious left ventricular failure. More recent studies have confirmed the general applicability of these findings to more usual forms of exercise such as cycling or walking but have also shown a number of variations of behavior in special classes of hypertensive patient. One difficulty in this work has been the determination of the normal cardiovascular response to exercise in different age groups, but this has now been clarified to some extent both for the bicycle ergometer[3] and the treadmill.

Investigation of the resting circulatory changes in mild hypertensive subjects has shown a tendency to an abnormally high cardiac output and a systemic resistance close to the normal range.[4] There is little evidence of hypertensive cardiac, retinal, or renal changes in these patients and there is a tendency for the hypertension to be more labile than usual. However, other work suggests that only a minority of early labile hypertensives have an abnormally high resting cardiac output. On exercise, the cardiac output rises and the systemic resistance falls in these patients in the same way as in normal subjects. There is evidence that the disease process in such patients may progress to a more characteristic hypertensive pattern with a normal cardiac output and a raised peripheral resistance. These findings lend support to the hypothesis that the cardiovascular changes in hypertension consist primarily of an increase in cardiac output followed by an adaptive response in the peripheral vessels producing an increase in resistance and a subsequent fall in output. An initial increase in cardiac output might be expected if the disease process affected capacitance vessels at an early stage. The abnormally large response to an increase in plasma volume that is found in hypertensive patients may be explained in a similar way.[12] The finding of an abnormally high resting cardiac output in renovascular hypertension[13] suggests that renal ischemia may be responsible for the hemodynamic changes. The increased output evidently persists in renal hypertensives, but a similar process may initiate the circulatory disturbance in essential hypertension.

When severe and persistent hypertension has led to considerable disturbance of left

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ventricular function the resting cardiac output tends to be reduced[2,4,12] and in some patients the response to exercise is subnormal In these patients, the peripheral resistance remains substantially raised both at rest and on exercise and the blood pressure is usually high Nevertheless, the effect of progressive changes in the peripheral vessels may be masked by a reduction in cardiac output in severe hypertension and the blood pressure alone may not give adequate evidence of the advance of the disease. One study[11] has shown a high cardiac output in severe hypertensive patients but this has not been confirmed It was suggested that the high output in these patients might be due to secondary hyperaldosteronism

The response of the peripheral vessels to the increase in cardiac output is surprisingly normal in hypertension. The relative increase in systolic pressure is usually a little greater than in normal subjects and the diastolic pressure shows relatively little change There is clearly extensive peripheral vasodilatation to accommodate the greater blood flow during exercise indicating that the vascular disease does not prevent an increase in the caliber of the vessels at least in some parts of the circulation In his study of the distribution of the peripheral blood flow in patients with hypertension Brod[5] found a tendency to vasodilatation in muscle in spite of the over all increase in peripheral resistance and the evidence of vasoconstriction in the viscera and skin It might be expected that the vasodilatation of exercise would similarly be largely confined to the vessels of skeletal muscle, although the myocardium and skin may also be involved with relatively little change or even vasoconstriction elsewhere. Consideration of the effects of two groups of resistances in parallel suggests that a normal degree of vasodilatation in muscle and skin to accommodate the increase in cardiac output during exercise would largely obliterate the effects of the raised resistance in other vascular beds on the blood pressure. As hypertension persists during exercise it seems likely that there is some residual abnormality of resistance even in muscle and skin vessels. The disturbance in circulatory control which allows a raised blood pressure at rest persists on exercise in spite of the widespread vasodilatation needed to accommodate the increased cardiac output.

The reduction in incidence of left ventricular failure and cerebral hemorrhage when high blood pressure is treated effectively suggests that these complications are directly related to the level of the arterial pressure.[15] The work load placed on the left ventricular muscle and the tension in the wall of the cerebral arteries are both determined by the arterial pressure. As patients spend much of their time asleep or at rest, it has been suggested that the 'basal blood pressure measured under these circumstances, is the main determinant of the prognosis. There is, in fact, excellent evidence to support this hypothesis.[1] The wide variations in response to anxiety and other stimuli have been thought to make the casual blood pressure, recorded without any preliminary rest a poor guide to the effects of hypertension Hypertensive patients who lead normal lives are, however physically active and depart considerably from the basal state for large portions of the day Under these circumstances, both the basal and the exercising pressure must influence the effect of hypertension on the left ventricle or the cerebral vessels.

Our own investigations in a limited number of patients[13] have shown a close relationship between the systolic pressure on exercise and the casual systolic pressure obtained in the outpatient clinic. The casual blood pressure seems therefore to be a useful guide to the blood pressure during exercise in the assessment of the hypertensive patient In patients leading normal lives the effective load on the circulation during waking hours is probably more nearly represented by the casual than the basal blood pressure, and both factors should be taken into consideration We have not found a progressive rise in systolic pressure at increasing work loads during exercise on the treadmill our findings differing in this respect from other work in which a bicycle ergometer was used[2] The vasoconstrictor effect of sustained hand-grip[17] while cycling may be responsible for this discrepancy As pressures on moderately strenuous exercise are

similar to those found during minor exertion there seems little advantage in advising the avoidance of normal levels of physical activity in hypertensive patients *unless* there is left ventricular failure when a moderate increase in left ventricular work may be of critical importance.

We were interested to find that our patients with labile hypertension who had pressures near the conventional normal range after a few days in the hospital showed similar pressures on exercise to those found in patients with more fixed hypertension. The cardiac output was not unduly low at rest in the labile hypertensives, indicating that the fall in pressure was due to peripheral vascular changes. There seems no question of any change in circulating blood volume, or in the degree of hydration of the arteriolar wall as the effect was promptly reversed by exercise. The cardiac output, and hence the peripheral resistance, were almost identical on exercise in the labile and fixed hypertensives and left ventricular work as determined from the pressure time per minute was also similar in the two groups.

It must be emphasized that these labile patients were not thought to have mild or uncomplicated disease but often had evidence of cardiac or retinal effects from the hypertension. Certainly in this group, labile hypertension cannot necessarily be regarded as a benign form of the condition although the near normal basal pressures might suggest that the hypertension was too mild to require treatment. A better estimate of prognosis might be expected from the casual blood pressure than from the basal values in these patients, and the return of the hypertension when the patient exercises suggests that some advantage might be expected from hypotensive treatment.

Preliminary studies of the hemodynamic response to hypotensive drugs during walking exercise on the treadmill indicate that a reduction in cardiac output at rest and on exercise plays a major part in the response to many agents. Selective cardiac sympathetic blockade with propranolol produced a substantial fall in blood pressure of similar degree at rest and on exercise mediated entirely by a reduction in cardiac output; there was no change in the peripheral resistance. A similar response has been reported at rest by other workers. Bethanidine on the other hand although it produced a little fall in cardiac output in the supine position had a much greater effect on the blood pressure and cardiac output in the erect position both at rest and during exercise. The fall in blood pressure during exercise was so great that it was difficult to produce a reasonable fall in the supine resting pressure without a risk of syncope on exertion. In addition to these effects, there was a tendency for the peripheral resistance to fall during exercise after bethanidine suggesting that vasodilatation in the arterioles was playing a part in the response.

The measurement of cardiac output and systemic resistance has given valuable insight into the state of the circulation in hypertension, and the assessment of the response to exercise is an essential part of the evaluation of the cardiovascular changes in this condition and the response to treatment.

REFERENCES

1. Varnauskas, E. Studies in hypertensive cardiovascular disease with special reference to cardiac function, Scandinav. J. Clin. & Lab. Invest. 7 (Suppl. 17): 1955.
2. Taylor, S. H., Donald, K. W., and Bishop, J. M. Circulatory studies in hypertensive patients at rest and during exercise. Clin. Sc. 16:351, 1957.
3. Strandell, T. Circulatory studies on healthy old men, Acta med. scandinav. 175 (Suppl. 414):1-44, 1964.
4. Sannerstedt, R. Hemodynamic response to exercise in patients with arterial hypertension. Acta med. scandinav. 180 (Suppl. 458): 1966.
5. Hanson, J. S., Tabakin, B. S., and Levy, A. M. Comparison of cardiorespiratory response to graded upright exercise of normal men aged 20-29 and 30-39. Brit. Heart J. 28:557, 1966.
6. Eich, R. H., Peters, R. J., Cuddy, R. P., Smulyan, H., and Lyons, R. H. The hemodynamics in labile hypertension. Am. Heart J. 63:188, 1962.
7. Bello, C. T., Sevy, R. W., and Harakal, C. Varying hemodynamic patterns in essential hypertension. Am. J. M. Sc. 250:58, 1965.
7. Levy, A. M., Tabakin, B. S., and Hanson, J. S. Hemodynamic response to graded treadmill exercise in young untreated labile hypertensive patients, Circulation 35:1063, 1967.
8. Eich, R. H., Cuddy, R. P., Smulyan, H., and Lyons, R. H. Hemodynamics in labile hypertension: follow-up study. Circulation 34:299, 1966.

9. Bello, C. T., Sevy, R. W., Harakal, C., and Hillyer, P. N.: Relationship between clinical severity of disease and hemodynamic patterns in essential hypertension, Am. J. M. Sc. 253: 194, 1967.
10. Ledingham, J. M., and Cohen, R. D.: Changes in the extracellular fluid volume and cardiac output during the development of experimental renal hypertension, Canad. M. A. J. 90:292, 1964.
11. Finckielman, S., Worcel, M., and Agrest, A.: Hemodynamic patterns in essential hypertension, Circulation 31:356, 1965.
12. Ulrych, M., Hofman, J., and Hejl, Z.: Cardiac and renal hyperresponsiveness to acute plasma volume expansion in hypertension, Am. Heart J. 68:193, 1964.
12a. Frohlich, E. D., Ulrych, M., Tarazi, R. C., Dustan, H. P., and Page, I. H.: A hemodynamic comparison of essential and renovascular hypertension: cardiac output and total peripheral resistance, supine and tilted patients, Circulation 35:289, 1967.
13. Hamer, J., Fleming, J., and Shinebourne, E.: Effect of walking on blood pressure in systemic hypertension, Lancet 2:114, 1967.
14. Brod, J.: Hemodynamic basis of acute pressor reactions and hypertension, Brit. Heart J. 25:227, 1963.
15. Hodge, J. V., McQueen, E. G., and Smirk, H.: Results of hypotensive therapy in arterial hypertension, Brit. M. J. 1:1, 1961.
16. Smirk, F. H.: High arterial pressure, Oxford, 1957, Oxford University Press.
17. Lind, A. R., Taylor, S. H., Humphreys, P. W., Kennelly, B. M., and Donald, K. W.: The circulatory effects of sustained voluntary muscle contraction, Clin. Sc. 27:229, 1964.
18. Shinebourne, E., Fleming, J., and Hamer, J.: Effects of beta-adrenergic blockade during exercise in hypertensive and ischaemic heart disease, Lancet 2:1217, 1967.

Clinical communications

Electrocardiographic abnormalities induced by thioridazine (Mellaril)

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Kelly and associates first reported striking T wave abnormalities and two fatal cases of ventricular tachycardia associated with complete A-V dissociation in a series of patients who were taking thioridazine (Mellaril). These observations were later extended by Ban and St. Jean[2,3] who found similar electrocardiographic abnormalities in emotionally disturbed patients who were taking other members of the phenothiazine group of drugs, i.e., chloropromazine (Thorazine) and triflu operazine (Stelazine). Two instances of thioridazine-induced ventricular tachycardia with favorable outcomes also have been reported.[4] Because of the paucity of reports in the American literature emphasizing the electrocardiographic abnormalities that may be induced by these commonly prescribed drugs, it was thought worthwhile to record the present observation of thioridazine-induced electrocardiographic changes in a child who ingested a large quantity of the drug in a suicide attempt.

Case report

A 12-year-old Puerto Rican boy (P. T., RUSAH T3199) had been in excellent health until 24 hours prior to hospitalization, at which time an acute situational depressive reaction developed and he ingested an estimated 4,000 mg. of his mother's thioridazine in a suicide attempt. He was found to be semicomatose with a blood pressure of 130/80, temperature of 101° F., and pulse of 130 per minute and regular. Other positive physical findings at this time were slightly decreased breath sounds with a few râles at the left base and a distended bladder. Cardiac examination was unremarkable. An osmotic diuresis was induced with 25 Gm. of intravenous mannitol after urethral catheterization. After the administration of intravenous fluids and antibiotics he became afebrile and responsive and made an uneventful recovery over the next seven days.

Laboratory studies showed a normal urinalysis, complete blood count, blood urea nitrogen, blood sugar, serial serum sodium, potassium, chloride, calcium, and phosphorus. Chest x-ray revealed a small patchy infiltrate in the left chest. The admission electrocardiogram (ECG) on May 16, 1967 (Fig. 1) showed a sinus tachycardia of 138 per minute and slightly lowered T waves, while the Q-T interval could not be accurately measured because of T-P fusion. Two days later on May 18, 1967 (Fig. 2) the rate had slowed to 108 per minute and the Q-T interval was slightly prolonged to 0.38 second (QTc of 0.30 second). T waves were broadened, flattened, and "bifid" or double-humped, especially in Leads II, V, V and V. Inversion of T V V with convex S-T segments and inverted to diphasic T V-V were also striking changes. Four days after admission on May 20, 1967 (Fig. 3), these abnormalities disappeared and there was a normal ECG.

Discussion

Thioridazine-induced T wave abnormalities may result from as little as 200 mg

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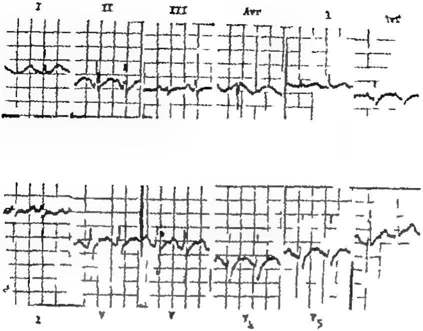

Fig. 1 ECG approximately 24 hours after thioridazine (Mellaril) ingestion

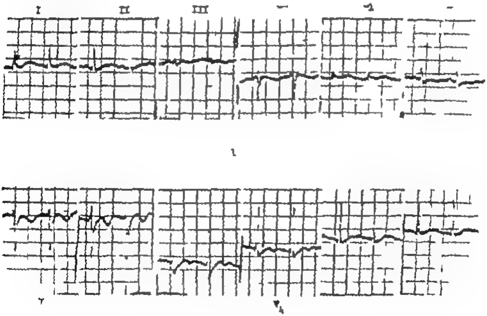

Fig. 2 ECG 48 hours after thioridazine (Mellaril) ingestion.

of the drug in 24 hours.[1] Although the ventricular arrhythmias have occurred in patients taking higher daily doses (600 to 3,600 mg.), it is not known if this serious complication is dose related.

The effects on repolarization have been likened to the quinidine or procaine amide effect,[1] yet unlike these drugs, thioridazine does not prolong the QRS, except of course in the ventricular arrhythmias. Likewise, it has been found to possess quinidine-like antiarrhythmic properties against various atrial and ventricular arrhythmias in experimental dogs.[6] Its clinical application as an antiarrhythmic agent remains an interesting possibility.

Fig. 3. ECG 4 days after thioridazine (Mellaril) ingestion.

As seen in this case, the usual electrocardiographic abnormality induced by thioridazine is "blunted," flattened, or bifid, and occasionally inverted T waves in the anterior septal region with a convex contour. Others have described the decreased T wave as being notched or double-humped, forming the proximal hump and a positive U wave forms the distal hump.[1,2,4] These changes may simulate the electrocardiographic changes of hypokalemia; however serum electrolytes and the S-T segments are normal. Prolongation of the Q-T interval is the result of the broadened T wave. Although similar repolarization abnormalities may be seen in patients taking the other phenothiazines, the effect is not as pronounced and frequent as with thioridazine. These changes are reversible upon discontinuing the drugs.

The most likely explanation for the phenothiazine induced electrocardiographic changes is a direct drug effect upon the myocardium, especially in view of the experimental evidence supporting their quinidine like activity. Likewise, the deposition of an acid mucopolysaccharide about intramyocardial and subendocardial capillary-arterioles has been found in patients who were taking phenothiazines and died unexpectedly and suddenly. Various arrhythmias and T wave changes had been present prior to death. Similar lesions could be produced in experimental animals fed phenothiazines and subjected to chronic stress. Epinephrine and norepinephrine or the adrenergic blocking action of the phenothiazines was implicated as the cause of these pathological lesions. On the other hand, some feel that this effect may be due to stimulation of higher central nervous system autonomic centers by the drugs, thus secondarily affecting ventricular repolarization[6] or actually may not necessarily be drug related since it is said that 15 per cent of a group of mentally disturbed patients, many of whom were not taking phenothiazines, may exhibit heteromorphic T wave abnormalities.

Summary

A case of thioridazine-induced electrocardiographic abnormalities in a 12 year old boy who ingested a large quantity of the drug is presented. T waves were flattened, broadened, notched, and inverted in the anterior septal precordial leads. The Q-T interval was slightly prolonged while the QRS and S-T segments were unchanged. These changes reverted to normal in approximately four days.

REFERENCES

1. Kelly, H. G., Fay, J. E., and Laverty, S. G.: Thioridazine hydrochloride (Mellaril): Its effect on the electrocardiogram and a [illegible] of [illegible] fatalities with electrocardi[illegible] normalities, Canad. M. A. J. 89

2. Ban, T A and St Jean A. The effect of phenothiazines on the electrocardiogram Canad. M. A. J 91:537 1964
3. Ban T A Electrocardiographic changes induced by phenothiazine drugs, AM HEART J 70:575 1965.
4. Schoonmaker F W Osteen, R. T and Greenfield, J J C Thioridazine (Mellaril) induced ventricular tachycardia controlled with an artificial pacemaker Ann. I t Med. 65 1076, 1966
5. Desautels, S., Filteau, C and St. Jean, A.: Ventricular tachycardia associated with administration of thioridazine hydrochloride (Mellaril) Canad. M. A. J 90 1030, 1964
6. Madan, B R. and Pendse, V K.: Antiarrhythmic activity of thioridazine hydrochloride (Mellaril) Am. J Cardiol 11 78, 1963.
7. Richardson, H L., Graupner K. I and Richardson, M E. Intramyocardial lesions in patients dying suddenly and unexpectedly J.A.M.A. 195:254 1966
8. Wendkos, M H Thioridazine and electrocardiographic abnormalities, Canad. M A J 89 1296 1963

Interatrial septal defect and pericardial disease

Coincidence or causal relationship?

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The coexistence of an interatrial septal defect (IASD) and pericardial constriction, adhesion, or effusion has been described[illegible] and commented upon.[illegible] It has been stated that an adherent pericardium, very much like valvular abnormalities, is a frequent accompaniment of IASD.[illegible] An explanation for the association has not been forwarded; contrariwise, surprise has been expressed that one does not see the combination more often considering the relatively frequent occurrence of rheumatic heart disease in IASD. More recently, mere chance relationship has been held responsible for this combination[illegible] which was regarded as clinically important by the same authors.

The simultaneous occurrence of IASD and pericardial disease seems to be widely unrecognized among clinicians as well as pathologists, and yet, the condition deserves attention. The diagnosis of IASD nowadays precipitates itself in most instances in surgical considerations where preoperative recognition of pericardial disease, especially constriction, is necessary to minimize the risk of surgical intervention.[2] Implications regarding general management of such patients are obvious.

We had opportunity to observe four patients with IASD and pericardial disease personally. In three of these, the combination had attained clinical significance: pericarditis progressing into constriction (Case 1), large effusion (Case 2), and a peculiar kind of chronic pericarditis with persistent friction rub (Case 4).

A review of the literature prompted by this experience yielded 63 such cases recorded, in by far the most of which pericardial pathology was listed as an incidental finding.

In an attempt to outline pathogenic aspects of the condition, we have remained unable to answer the question regarding causal relationship, but we believe that there is good reason for pericardial disease *to develop in IASD*. We hope to stimulate interest and awareness of a condition which merits the clinician's attention.

Case reports

Case 1. Patient A. G. (WRGH No. 4727-035) had been asymptomatic and had served on active duty

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Fig. 1. Chest roentgenograms of patient A. G. *A*, Routine chest film taken at *age 22 before pericarditis appeared*, showing increased pulmonary vascularity of central left-to-right shunt. *B*, Film taken at time of pericarditis with large effusion. *C*, Film taken five years later when pericardial constriction had developed. Note inconspicuous right atrium. IASD with 5:1 left to-right shunt was diagnosed at this time.

Fig. 2. Patient A. G. Cardiac catheterization data

Chamber	*Pressure* (*mm. Hg*)	*O₂ saturation* (%)
RSVC		59.9
RA	20/12†	87.7
RV	30/10–15†	91.2
PA	28/15†	91.3
LA	23/12†	96.4
LV	134/15†	99.4
RPV		98.5

*Systemic blood flow 2.5 L. per minute; pulmonary blood flow 10 L. per minute; Q_P/Q_S 5:1.

†Pressures are almost identical. Findings consistent with constrictive pericarditis as documented at operation in this patient.

Fig. 3. Chest roentgenogram of patient H. W. demonstrating extreme enlargement of the cardiac silhouette, compatible with IASD and pericardial effusion. Note also aneurysmally dilated pulmonary arteries consistent with large atrial left-to-right shunt.

with the armed forces until the age of 22 years, when he developed fever, chest pain, and dyspnea. Acute, nonspecific pericarditis was diagnosed during the course of which large serosanguineous pericardial effusion developed (Fig. 1). For the ensuing five years, the patient remained dyspneic and eventually developed congestive heart failure (CHF). Cardiac evaluation, including cardiac catheterization, then revealed the presence of constrictive pericarditis as well as congenital heart disease consisting of IASD with large left-to-right shunt further aggravated by anomalous pulmonary venous drainage of the right lung and a persistent left superior vena cava. Cardiac catheterization data are shown in Fig. 2. The patient underwent open heart surgery at which time a markedly thickened pericardium with calcified plaques was found, constricting mainly the right heart. The small size of the right atrium (RA) was believed to be the result of rather marked pericardial constriction of this chamber. A 2.5 cm. large septum secundum type of IASD was found together with complete anomalous drainage of the right pulmonary veins which entered in two separate trunks, an inferior one connecting to the lateral wall of the RA, and a superior one draining into the superior vena cava. A persistent left superior vena cava was seen to empty into the coronary sinus. The thickened pericardium was removed, the left superior vena cava ligated, and a Ivalon patch placed in such a manner as to channel the right pulmonary vein blood through the IASD into the left atrium (LA). The patient did well postoperatively except for a transient postcardiotomy reaction.

Comment. Pericarditis of undetermined etiology had within five years led to constriction and set off cardiac decompensation in a previously well-tolerated IASD. In spite of the large left to-right shunt resulting from IASD and anomalous pulmonary venous drainage, the RA was of small size but seemed to be the site of major pericardial involvement.

The association of IASD and pericardial constriction was diagnosed clinically in this patient and corroborated by cardiac catheterization. As a result, corrective operation was successfully planned and performed with excellent relief of both hemodynamic abnormalities.

Case 2. H. W. (WHC No. 31 72 70), a 37-year-old

Fig. 4. Chest roentgenograms of patient E. T. showing marked cardiomegaly with four-chamber enlargement due to combination of large IASD with mitral and tricuspid incompetence. Increased pulmonary vascularity. No indication of pericardial disease by x-ray or ECG or clinically; diffuse pericardial fibrosis and adhesion found at autopsy.

housewife, had a history of dyspnea, fatigue, recurrent bronchopulmonary infections, and CHF for many years. Recurrent tachyarrhythmias, cyanosis, and edema had led to deterioration and death.

At autopsy, the pericardium contained 800 ml. of serosanguineous fluid, but showed no signs of inflammation. There was marked cardiomegaly (Fig. 3) with enlargement of all four chambers, especially the very considerably dilated RA. The atria were in open communication through a patent foramen ovale, 3.5 by 1.5 cm. wide, with a crescentic remnant of the septum secundum. The mitral valve was moderately stenosed and showed irregular fibrous thickening of the free margins with commissural fusion and thick and shortened chordae tendineae, characteristic of old rheumatic valvulitis. The aortic valve was congenitally bicuspid with fusion of the right and the noncoronary leaflet. The tricuspid valve was intact, but the valve ring was sufficiently dilated to render the valve incompetent. The aorta was small, the pulmonary artery aneurysmally dilated (Fig. 3).

Comment. This patient had IASD with large left-to-right shunt complicated by rheumatic mitral stenosis, functional tricuspid incompetence, and congenital aortic stenosis. Large pericardial effusion had developed insidiously. As will be discussed below, the exceptional size of the RA resulting from large atrial shunt and mitral and tricuspid valve dysfunction may relate to the development of the effusion.

Case 3. E. T. (WHC No. 27-44-81), a 39-year-old housewife, had had frequent respiratory tract infections in childhood, but had remained otherwise asymptomatic until only recently when atrial fibrillation and CHF appeared, leading to rapid deterioration and death.

Autopsy showed complete obliteration of the pericardial space by dense fibrous adhesions without evidence of constriction. The heart weighed 700 grams, the largest chambers were right and left atrium (Fig. 4). There was a large interatrial communication through multiple defects of the septum. A 3 by 3.5 cm. foramen ovale was crossed by a narrow bandlike structure with multiple small perforations. A 1.5 by 1 cm. defect was located just posteriorly to the secundum defect. The leaflets of the mitral and tricuspid valve were markedly thickened and shortened, and the chordae tendineae partially fused, short, and thickened. The result was rather marked mitral and tricuspid incompetence. Several pleural adhesions were found bilaterally together with bronchopneumonia and pulmonary infarction. The valve lesions were considered rheumatic.

Comment. The combination of large IASD and organic mitral and tricuspid incompetence had resulted in marked biatrial, especially right atrial enlargement, together with biventricular dilatation. Diffuse pericardial adhesion had gone clinically unrecognized and had apparently been without consequences. Whether etiological mechanisms relating to atrial enlargement had been operative in this patient remains speculative, as in Case 2. Pericardial adhesions might have been residual from rheumatic carditis, or referable to pleuropulmonary infections, transmitted by contiguity, thus linking the pericardial lesion to the atrial shunt.

Case 4. R. K. (GUH No. 220870),* a 36-year-old

*This patient was referred to Georgetown University Hospital by Dr. C. Vincent Townsend of Martinsburg, W. Va. We are indebted to him and to Dr. W. Proctor Harvey for permission to include this case.

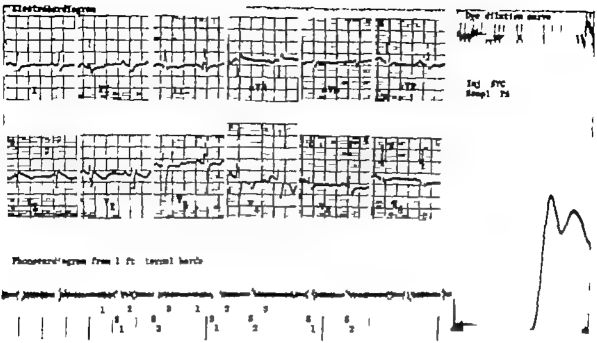

Fig. 5. Patient R. K. ECG showing right ventricular conduction defect of IASD and ST-T changes in precordial leads compatible with pericarditis. Phonocardiogram (bottom strip) demonstrates (1) atrial systolic, (2) ventricular systolic, and (3) ventricular diastolic components of typical 3-component pericardial friction rub. Dye dilution curve at upper right, obtained at cardiac catheterization, shows left-to-right shunt which was localized at the atrial level by catheter passage and N_2O-inhalation test, the latter indicating pulmonary blood flow as 1.4:1 in excess of systemic flow.

mother of t had been well, except for an episode of pleuritis at age 21 until January 1962 when she developed pericarditis with malaise and epigastrial and chest discomfort associated with left arm pain, soon followed by fatigue, dyspnea, and recurrent palpitations. Evaluation revealed loud pericardial friction rub, increased precordial right ventricular impulse, and fixed splitting of the second heart sound. Cardiac catheterization established the presence of an IASD, probably of the septum secundum type, with small left-to-right shunt and normal right heart pressures (Fig. 5). A specific etiology of the pericarditis could not be found despite of extensive investigation; therapeutic trial with steroids did not influence the friction rub which continued to be present under continuous observation for the ensuing five years, while other symptoms of pericardial disease had abated early with the initial episode. Mild chronic fatigue, occasional dyspnea, and palpitations are her only symptoms at the present time and seem related to the IASD.

Comment. Although morphological proof of pericarditis was not obtained in this patient, the clinical diagnosis seemed inescapable. It is of note that the characteristic pericardial friction rub has persisted unchanged over a period of now five years—a remarkable and unexplained observation unique in our experience with pericarditis. Note further that the development of pericarditis coincided with the onset of cardiac symptoms referable to the IASD, as also seen in Case 1.

Review of the literature. Descriptions of cases of IASD and pericardial diseases were found in 32 publications. While most of the information was contained in review articles on the subject of IASD, a considerable number of cases were found in publications concerned with Lutembacher's syndrome, including Lutembacher's original patient. Comments on the association of IASD and pericardial disease were very few[1,8,21,28] and neither a review of the subject nor data regarding incidence or significance of the condition were available.

Criteria for inclusion in this study were an IASD of more than 2 cm in diameter and autopsy evidence of inflammatory pericardial changes or noninflammatory pericardial effusion of more than 75 ml. By way of exception, two cases with valve patency of the foramen ovale were included. One had anomalous pulmonary venous connection to the RA, thus providing the hemodynamic e at of IASD (Case 56). The other rlying Ebstein's malformation as oped right to-

left shunting through the foramen ovale due to chronically increased right atrial pressure (Case 62)

The cases collected are described in Table I and summarized in Table II including our four patients.

Average age at the time of death in the deceased patients was 38 years, and is thus in accordance with the life expectancy of patients with uncomplicated IASD of 33 to 49 years.[illegible] Hence the incidence of pericardial disease did not appear to have significantly altered the prognosis. Sex distribution was likewise as observed in uncomplicated IASD [illegible] The majority of patients had septum secundum type defects. Septum primum posterior or superior multiple or complete defects were encountered as to be expected in any population of IASD The size of the defect and of the heart chambers was difficult to assess from the information available. Using an arbitrary classification (Tables I and II) we conclude that most of the defects were 'large to very large and the RA mostly very large. Information regarding the size of the LA was given too infrequently to allow conclusions. In several instances, however the LA was described as enlarged usually where mitral valve lesions coexisted

The pericardium showed signs of old or active nonspecific inflammation in most of the cases (77 per cent) Complete obliteration had occurred in 12 cases and had led to constriction in six. In five instances, a specific etiology could be substantiated tuberculosis in two, rheumatic carditis in two systemic lupus erythematosus disseminatus in one.

Associated congenital cardiovascular defects were rare. In three cases anomalously draining pulmonary veins had contributed to the left to-right shunt (Cases 5 56 and our Case 1) in one a patent ductus arteriosus (Case 62) was responsible for increased pulmonary blood flow and in four patients complex AV-canal type deformities were present with AV valve incompetence and shunting at the atrial and ventricular level (Cases 1 2 4 and 40)

Abnormalities of the cardiac valves, especially the mitral and tricuspid valves were encountered frequently (62 per cent) often involving two or more valves. The etiology of these lesions was not uniform In patients with ostium primum IASD deformities of the AV valves were most often part of the congenital defect. However chronic valvulitis was found to be responsible for the valve lesions in the great majority of the cases a rheumatic etiology was postulated in most of these on the basis of the pathological appearance of the lesions and corroborated as such by a history of acute rheumatic fever or streptococcal infection in 28 per cent. The over-all incidence of streptococcal infection was 14 per cent. The prevalence of rheumatic endocarditis in this study is comparable to figures given for IASD in general (40 to 77 per cent) [illegible] Subacute bacterial endocarditis is known to be uncommon in IASD [illegible] Three of the reported cases had coexistent pericardial disease and appear in this review (cases 21 32 and 40)

Nonspecific, old or active pleuropulmonary inflammatory processes were seen frequently and were further corroborated by the characteristic anamnestic information of recurrent respiratory tract infections in many patients.

Discussion

The prevalence of pericardial disease in IASD is difficult to assess. Rokitansky in his classical monograph Die Scheidewaende des Herzens in 1875 described 20 cases of IASD 12 of which had pericardial disease. Only a few reports have appeared since that time and many a review of IASD including current text books, does not even mention this association It is possible that the over all incidence of pericarditis has declined since Rokitansky s days parallel to the decline in infectious diseases. Nevertheless the association of pericardial disease and IASD appears to be more common than generally appreciated From our review of the literature, we would estimate the autopsy incidence of pericardial lesions to lie in the vicinity of 12 per cent of all cases of IASD It has to be said however that situations where pericardial adhesion constriction or effusion had led to further embarrassment of cardiac function or had otherwise become clinically significant were less common. Surgical closure of IASD is

Table I Summary of cases reviewed

No.	Author	Year	Case	Age	Sex	IASD†	Pericardium‡	Etiology§
1	Rokitansky	1875	1	35	M	1 2.8 cm.	Ef 90 ml., F	Cong infl.
2			2	50	M	1 3 cm	Ef 60 ml., FA	Infl.
3			5	22	F	1 2 x 2.5 cm	Ef 1,000 ml.	Infl.
4			6	60	F	1 9 x 5 cm	Ef 60 ml., F	Infl.
5			8	50	F	2° 5 7 cm.	Ef 50 ml., FA	Infl.
6			9	20	F	2° compl.	FA, Ca	Infl.
7			11	23	F	2° 3.3 cm.	FA, Ca diff	Infl. tbc.
8			12	44	M	2° 3.5 cm	Ef F	Infl.
9			15	21	M	2° large	Ef 90 ml., F	Cong
10			16	43	M	Mult. large	Ef 30 ml. F	Infl.
11			19	32	F	2°	Ef F	Infl.
12			20	56	F	2° 2 cm.	FA, Ca	Infl.
13	Chouppe	1872		48	F	2° 2 x 1.5 cm.	FA	Infl.
14	Gagnoux	1910		?	M	2° large	Constr	Infl. tbc.
15	Lutembacher[3]	1916		61	F	2° 3.5 x 4 cm.	Ef 200 ml.	Cong
16	Moukhtar[4]	1926		33	F	2° 3.5 x 2 cm.	FA	Infl.
17	Jones[5]	1928		28	F	1 2° 4 cm	Ef 100 ml., F	Infl.
18	Jerofejeff[7]	1933		31	M	2° 4 cm.	Ef F	Infl. rheum.?
19	Roesler[8]	1934		18	F	2° mult.	Ef 100 ml., FA	Infl.
20	Quirno and Battro[9]	1936		22	M	2° large	Constr	Infl.
21	Sailer[4]	1936	1	43	M	1 3 cm.	Ef 130 ml F	Infl.
22	Cossio and Berconsky	1936		25	M	Single atr	FA, diff	Infl. rheum.
23	Cossio and Arana	1937	1	23	M	2° 4 cm.	FA	Infl. rheum.
24	Battro and Serna	1937	1	26	M	Single atr	FA, diff	Infl.
25			2	35	F	2° large	FA diff	Infl.
26	Taussig and co-workers[13]	1938	4	9½	F	2° 3 cm	Ef 150 ml., F	Infl.
27	Tinney[12]	1940	1	76	M	2° 4 5 cm.	Ef small	Cong.
28			2	47	M	2° 4.5 cm.	Ef small	Cong
29	Bedford and co-workers[14]	1941	8	43	F	2° 7 x 4 cm.	Ef 90 ml., FA	Infl
30	Laubry[*]	1941	4	47	M	2° 5 cm.	FA diff	Infl
31	Tinney and Barnes[16]	1942	1	50	M	2° mult., 5 cm.	Ef 300 ml., F	Cong
32			2	36	M	2° 3 x 4 cm.	Ef 300 ml., F	Cong
33			3	63	M	2° 2 cm.	Ef 75 ml.	Cong
34			4	56	F	2° 3 x 2.5 cm	Ef 75 ml.	Cong
35	Jouve	1945		27	F	2° 5 cm.	Ef	Cong
36	Chamagne	1945		34	F	Post., large	FA	Infl. rheum.
37	Burrett and White[17]	1945	2	43	F	2° 3.5 cm.	FA	Infl.
38	Ravault[*]	1946		45	M	2° 2 cm.	FA	Infl.
39	White[18]	1951		?	?	IASD	Constr	Infl.
40	Cahen and co-workers[19]	1952	2	21	F	1 large	Ef 800 ml.	Infl.
41	Soulié and co-workers	1954	1	54	F	2° 2 cm.	Ef 200 ml.	?
42			2	50	F	2° 5 cm.	Ef 300 ml.	?
43			3	19	F	2° large	FA, diff.	Infl.
44	Perrot[20]	1958	116	65	M	IASD	Ca	Infl
45	Davidsen[21]	1960	3	20	F	2° large	FA	Infl.
46			21	23	F	2° 3.3 cm.	FA	Infl.
47			26	40	M	1 7.8 cm.	FA	Infl.
48			109	23	M	2° 5 4 cm.	FA	Infl.
49			131	47	M	1 5 cm.	FA	Infl.

*Quoted from Bédard.
†Abbreviations: 1° ostium primum; 2° ostium secundum; post., posterior; sup. superior; mult., multiple; single atr complete IASD.
‡Pericardium: Ef effusion in milliliters; F fibrinous; A, adhesions; diff diffuse adhesions or complete obliteration of pericardial space; constr constrictive pericarditis; ca, calcification.
§Etiology: Infl., inflammatory; cong., congenital; SLE, systemic lupus erythematosus; tbc., tuberculous; rheum., rheumatic.
‖Size of heart chambers: 4, huge; 3, very large; 2, moderately large; 1, normal; 0, small.
¶Valvular lesions: MI, mitral; TV, tricuspid; AV, aortic; PV, pulmonic valve; MS, mitral stenosis; MI, mitral insufficiency; others accordingly. PDA, patent ductus arteriosus; LSVC, left superior vena cava.

Size of heart chambers‖				*Valvular lesions¶*	*Associated congenital defects*	*Pleuropulmonary disease*
RA	*RV*	*LA*	*LV*			
3	3	?	?	MV and TV thickened	AV-canal	—
3	3	?	?	MV and TV thickened	AV-canal	Emphysema
2	2	?	?	TV perforated	—	—
2	2	?	?	MV and TV thickened	AV-canal	—
3	3	2	2	—	—	Pleural adhesions
?	3	?	?	—	—	—
?	2	?	?	MV and TV thickened	—	Cavernous tbc.
?	3	?	?	—	—	—
?	?	?	?	—	—	Pneumonia
4	4	?	?	—	—	Bronchitis
2	2	?	?	MV and TV thickened	—	—
3	3	?	?	MV and TV thickened	—	—
3	3	?	2	MS and AS	—	?
?	?	?	?	?	?	Extensive, tbc.
4	4	3	0	MS	—	Emphysema, tbc.
4	3	2	?	—	RV aneurysm	—
3	3	2	?	MV and TV thickened	—	—
3	3	3	1	MS and MI rheum.	—	Pleural eff. and adhesions pneum.
4	4	1	0	MI and TI rheum.	—	Pleural eff
3	2	?	?	MS	—	Pleural eff and adhesions
4	4	2	?	Endocarditis MV	—	Pleural adhesions
4	3	2	3	MI, AS, AI rheum.	—	—
4	3	?	?	MS and AI, rheum.	—	Pleuroperic. adhesions
4	2	?	2	MI rheum.	—	Pleural eff and adhesions
4	2	?	?	MV and TV rheum.	—	Pleuroperic adhesions
3	3	0	0	MS, MI TV rheum.	Coarctation	Pneumonia
4	4	?	1	—	—	Pneumonia
3	3	?	?	—	—	Pleural eff
3	3	2	1	MS, TV rheum.	—	Pneumonia
?	?	?	?	—	—	—
4	4	2	2	MS and MI, TI P thick.	—	Pleural eff
?	3	?	2	MS and MI TI function endocarditis	—	Pleural eff
?	?	?	?	Ca AS	—	Pleuroperic. adhesions
?	?	?	?	—	—	—
3	3	?	?	—	—	Cavernous tbc.
3	3	2	2	—	—	Pleural adhesions
3	3	1	1	MV thickened	—	Tbc.
3	3	?	?	—	—	Pul emboli
?	?	?	?	?	?	?
?	?	?	?	Cleft MV and TV endocarditis	AV-canal	—
2	1	1	1	MS and AS, Ca rheum.	—	—
4	3	1	?	MS, Ca, TI	—	
4	4	3	?	MS, Ca	—	?
?	?	?	?	?	?	?
?	?	?	?	—	—	—
?	?	?	?	—	Anomal. LSVC	—
?	?	?	?	—	—	—
?	?	?	?	MI	—	—
?	?	?	?	—	—	—

Continued

Table I Summary of cases reviewed—cont'd

No.	Author	Year	Case	Age	Sex	IASD†	Pericardium‡	Etiology§
50			141	35	F	2° large	FA	Inf.
51			151	35	M	1 4 cm	FA	Inf.
52			167	59	F	Super 2 cm.	FA	Inf.
53			171	19	F	2° large	FA	Inf.
54				14	M	IASD	Acute peric	Inf.
55	Semler and co-workers	1960	11	17	M	2° large	Constr	Inf.
56			2	31	F	Valve pat	FA, diff	Inf.
57			3	33	M	2° moder	Constr Ca	Inf.
58			5	47	F	Post., 2 cm	Ef 2,000 ml.	Inf.
59			6	48	F	2° 6 x 4 cm.	Ef 1,300 ml.	Inf.
60	Mihailescu and co-workers	1962		46	F	2° ?	Constr Ca	Inf.
61	Marshall and Warden	1964	1	18	F	2° 2 x 3 cm	Ef large	Cong
62	Mamm and co-workers	1964		15	F	Valve pat	Ef large	Inf.
63	Yurchak and co-workers	1965		58	M	2° x 2.5 cm.	FA, constr	Inf., SLE
64	Just and Mattingly	1967	1	27	M	2° 2.5 cm	Constr Ca	Inf.
65		1967	2	37	F	2° 3.5 1 cm	Ef 800 ml.	Cong ?
66			3	39	F	Mult large	FA, diff	Inf.
67			4	36	F	2° small?	Chron. peric.	Inf.?

surprisingly often followed by postpericardiotomy reactions.[34] This complication had also occurred in one of our cases (Case 1).

In search for causative mechanisms the following considerations can be made. The right heart chambers are regularly, often very considerably, enlarged in IASD. Most of the cases complicated by pericardial disease in our review appeared to have very large right atria (Table II). Chronic right heart failure, organic or functional tricuspid incompetence as well as mitral valve lesions —the latter through augmentation of the left-to-right shunt—will only add to the load on the RA. Coexisting valvular defects were found in 62 per cent of the cases reviewed.

Diseases accompanied by chronically increased intra-atrial pressure and excessive right atrial enlargement are often complicated by pericardial effusion or fibrosis. Ebstein's malformation, a condition with typically very marked right atrial dilatation and regularly compounded by tricuspid incompetence, is known to be accompanied by pericardial disease.[37,38] Congenital pulmonic valve stenosis with massive right heart enlargement and failure can be complicated by pericardial effusion[39] (Case 4). Endomyocardial fibroelastosis of the right heart as it occurs in tropical Africa leads to progressive fibrosis and contraction of the right ventricle, resulting in loss of contractile function of this chamber, massive tricuspid incompetence, and very marked right atrial hypertrophy and dilatation.[40] The condition is regularly accompanied by large serosanguineous pericardial effusion and fibrosis.[34]

The mechanism of production of pericardial fluid is incompletely understood. It seems that both peri- and epicardium participate in transudative and exudative processes.[37] The RA harboring the sinoatrial node attracts a rich vascular, lymphatic, and neural supply, and thus occupies a unique position among the four heart chambers. The peculiar properties of the RA are further emphasized by the observation that experimental stretching of its wall stimulates secretion of the sodium-retaining hormone Aldosterone.[42] Furthermore, digital compression of the coronary sinus or tricuspid regurgitation alone, according to earlier work,[43] may

...nce of heart chambers‡				Valvular lesions	Associated congenital defects	Pleuropulmonary disease
RA	RV	LA	LV			
	?	?	?	—	—	—
?				—	—	—
			?	—	Anomal. pul. ven	—
				—	—	—
			?	MI and TI rheum	—	—
1	?		?		—	
2	1	2	2	?	Anomal. pul. ven	—
2	?		?	TI functional	—	—
	?		?		—	—
2	?		?	TI functional	—	—
2		?	?	—	—	—
3	3	3	3	MI rupt. chord	—	Pleural eff
2	1	1	1	TI PS	Elastin anom. PDA	—
?	2	1	1	MI AI TI rheum	—	Pleuropericarditis
2	1	1	1	—	LSVC	—
4	2	1	1	MS, rheum bicuspid AV	—	—
3	2	2	2	MI and TI rheum.	—	Pleural adhesions
2	1	1	1	—		

result in accumulation of pericardial effusion

We therefore speculate that factors related to abnormalities of the RA may play a role in the genesis of pericardial effusion in IASD a supposition awaiting experimental investigation

Chronically increased pulmonary blood flow as it occurs in IASD is well known to predispose to pulmonary infections which in turn are capable of initiating pericarditis by contiguity Such an explanation could be supported by the high incidence of pericardial disease in the early series reported by Rokitansky[3] in a period when the incidence of infections was high and antibiotic therapy was nonexistent If this were the only factor we should have witnessed a marked decrease in the association of pericardial disease during the past 20 years of antibiotic therapy (1948 to 1967) During this period a total of 29 cases were reported whereas in the preceding 40 year period (1908 to 1948) only 33 cases were reported Furthermore if chronically increased pulmonary blood flow and pulmonary infections were the dominant mechanisms, one would expect to find pericardial disease as frequent in the ventricular septal defect and the patent ductus arteriosus, which has not been reported to our knowledge

Rheumatic endocarditis is often considered to be a frequent accompaniment of IASD [?] The etiology of the commonly found deformities of the cardiac valves has been a matter of debate[44] the majority of them however are considered to be rheumatic in origin The then inferred rheumatic carditis would provide opportunity for the development of pericarditis [40]

In conclusion we therefore believe that there is ample opportunity for pericardial effusion adhesion or constriction to develop in IASD and we are in accord with Roesler[4] in our surprise that one does not see pericardial disease more often associated with IASD

Summary

Four patients of our own observation and 63 cases from the literature were reviewed illustrating the association of IASD and pericardial effusion adhesion or constriction In three of our four patients pericardial disease had assumed dimensions of

Table II. Summary of cases reviewed in Table I

	N	Per cent*
Cases	57	
Age (years)		
Range	9½–76	
Average	37	
Male patients	30	44
Female patient	37	56
IASD		
Septum secundum type defect	48	73
Septum primum type defect	9	14
Other defects (superior posterior)	3	5
Multiple defects or complete absence of IAS	7	9
Diameter of IASD		
Greater than 4 cm.	27	45
2 to 4 cm.	26	43
Less than 2 cm.	7	12
Size not certai	7	
Pericardium		
Effusion, congestive and/or inflammatory	29	44
Fibrosis and/or localized or diffuse adhesions	46	70
Calcification	7	10
Constriction	8	12
Nonspecific inflammatory etiology	52	78
Specific etiology		
Tuberculosis	2	
Lupus erythematosus disseminatus	1	
Rheumatic (proved)	2	
Right atrium		
"Giant	15	38
"Very large	19	46
Moderately large	7	16
Normal or small	1	
Undetermined	24	36
Associated valvular abnormalities	39	61
Mitral valve (alone or in combination)	33	51
Tricuspid valve (alone or in combination)	21	33
Multivalve involvement	22	33
Rheumatic etiology (history of rheumatic fever in 9)	20	32
Congenital or undetermined origin	18	29
Bacterial endocarditis	2	
Associated congenital cardiovascular defects	7	11

*Per cent figures refer to 100 per cent the number of cases for which the respective information as available not always to the total number of cases of the series

Table II Cont'd

	N	Per cent*
Pleuropulmonary disease		
Pleural effusion	8	12
Nonspecific, old or active inflammatory lesions	17	26
Tuberculosis	5	8

clinical importance or intensified progressive cardiac decompensation. One patient was of particular interest because of unusual persistence of a pericardial friction rub which has been present for now five years.

Pericardial disease appears to be relatively common in IASD as has occasionally been indicated in the literature and it is probably more frequent than chance relationship could account for

We have suggested that right atrial enlargement and chronic elevation of intraatrial pressure may play an important, yet ill-defined role in the genesis of pericardial effusion

Recurrent pulmonary infections common in conditions with augmented pulmonary blood flow and rheumatic heart disease provide opportunity for pericarditis to develop This may be an important factor

Chronic heart disease especially mitral and tricuspid incompetence or stenosis was frequently seen in the cases reviewed this may relate to the supposed mechanisms linking IASD and pericardial disease

The condition may be of considerable clinical importance and its recognition is essential for successful management and well planned surgical intervention

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REFERENCES

1 Rokitansky C. V : Die Defekte der Scheidewaende des Herzens, Wien, 1875 W Braumueller
2. Gignoux, ... Contribution à l'étude des com-

munications interauriculaires, Thèse de Lyon, 1910.
3. Lutembacher R. De la stenose mitrale avec communication interauriculaire, Arch mal. Coeur 9:237 1916.
4. Jonas, P Ein persistierendes Foramen primum bei einer Siebentgebaerenden, Arch. Gynaekol. 133:150, 1928.
5. Jerofejeff P Offenes Foramen ovale bei Mitral stenose, Frankfurter Ztschr P th 46:92, 1933
6. Roesler H. Interatrial septal defect, Arch. Int. Med. 54:339 1934.
7. Cosmo, P and Berconsky I. La Comunicacion interauricular y sinfisis pericardiaca, Rev Argent. Cardiol. 3:360, 1936.
8. Saller S. Mitral stenosis with interauricular insufficiency Am. J Pathol. 12:250 1936.
9. Quirno, N and Battro, A. Compresion cardiaca chronica, Prensa Med. Argent. 23 1972, 1936.
10. Battro, A., and Serna, A. de la Comunicacion interauricular Rev Argent. Cardiol. 3:417 1937
11. Cossio, P and Arana, R. S. Communication interauriculaire Bull. Acad. Nat. Med. 117:212, 1937
12. Taussig, H. B Harvey A. M and Follis, R. N Interauricular septal defect. Four cases, Bull. Johns Hopkins Hosp. 63:61 1938.
13. Tinney W S.: Interauricular septal defect, Arch. Int. Med. 66:807 1940.
14. Bedford, D E., Papp, C., and Parkinson, J Atrial septal defect, Brit. Heart J 3:37 1941
15. Laubry C., and Routier D La dilatation congenitale de l'artère pulmonaire, Bull. Acad. Méd. 125:126, 1941
16. Tinney W S., and Barnes, A. R. Interauricular septal defect, Minnesota Med. 25:637 1942.
17. Burrett, G. B. and White, P D Large interauricular septal defect with particular reference to diagnosis and longevity Report of two new cases, Am. J M Sc. 209:355, 1945.
18. Nérard, M A. Contribution à l'étude de la communication interauriculaire Thèse de Lyon, 1948.
19. White, P D Chronic constrictive pericarditis, Circulation 3 288, 1951
20. Cahen, P Froment, R., Gonin, A., and Traeger J Faux syndrome de Lutembacher par persistance de l'ostium primum avec scission de la valve mitrale interne Arch. mal. Coeur 45:203 1952.
21. Soulié, P Bouvrain, Y and Sibille, A. A propos de cinq observations de syndrome de Lutembacher, Arch. mal. Coeur 47:97 1954.
22. Pernot, P Étude de 166 cas de communications interauriculaires, Thèse de Paris, 1958.
23. Davidson, G. Atrial septal defect, Kopenhagen, 1960, Ejnar Munksgaards, Forlay
24. Semler H. J Brandenburg, R. O and Kirklin J W Pericardial disease complicating congenital heart lesions, Ann. Int. Med 53:494 1960.
25. Mihailescu, V V Efraim, M Enescu R., and Godreanu, R Consideratii asupra unui caz de paricardita la bolnava cu defect septal atrial, Med. Int. 24:999 1962.
26. Marshall, R. J and Warden, H E. Mitral valve disease complicated by left to right shunt at atrial level, Circulation 29:432, 1964
27. Masanti, J G Nevarret, E., Perez Acebo, J E., Malenchini, M and Belinsky A. Anomalia de Ebstein de la valvula tricuspide asociada derrame pericardico, Rev A. Med. Argent. 78:659 1964.
28. Yurchak, P M., Levine S. A., and Gorlin, R. Constrictive pericarditis complicating disseminated lupus erythematosus, Circulation 31 113 1965
29. Métianu, C., and Durand, M Les communications interauriculaires, Donzelot, E., and d'Allaines, F editors Traité des cardiopathies congénitales, Paris, 1964 Masson & Cie.
30. McGinn, S., and White, P D Interauricular septal defect associated with mitral stenosis, Am. Heart J 9:1 1933
31. Espino-Vela, J Rheumatic heart disease associated with atrial septal defect, Am Heart J 57 185 1959
32. Taussig, H B Congenital malformations of the heart, The Commonwealth Fund, 1960 Harvard University Press.
33. Sabatini, R., and Zirine, C. L cas de maladie d'Ebstein associé à une péricardite, Pediatria 16 730, 1959
34. Nadas, A. Pediatric cardiology Philadelphia, 1965 W B. Saunders Company
35. Abrahams, D G. Endomyocardial fibrosis of the right ventricle, Quart. J Med 31:1 1962
36. Abrahams, D G and Parry E. H. O Chronic pericardial effusion complicating endomyocardial fibrosis, Circulation 28:221 1963
37. Moenckeberg J G Henke F and Lubarsch O editors Handbuch der speziellen Anatomie und Histologie, Berlin 2:556, 1924
38. Anderson, C. H and McCally F Effect of atrial stretch on aldosterone secretion, Endocrinology 64:202 1959
39. Bouvrain, Y and Sibille A Les valvulites mitrales associées à la communication interauriculaire Sem Hôp Paris 30:3414 1954.
40. Connolly D C and Burchell, H B Pericarditis A ten year survey Am. J Cardiol 7 7 1961.

Rapid intracardiac pacing for treatment of recurrent ventricular tachyarrhythmias in the absence of heart block

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It is now well established that pacing the heart at a faster rate generally abolishes serious ventricular tachyarrhythmias when they occur in the setting of complete atrioventricular (A-V) block. Moreover, reports have recently appeared describing the value of rapid cardiac pacing to suppress serious ventricular arrhythmias refractory to usual pharmacologic treatment even in the presence of normal A-V conduction.

The two patients of Sowton and associates had recurrent ventricular tachycardia and ventricular fibrillation which could not be stopped with antiarrhythmic drugs. Electrode catheters were passed into the right ventricles and ventricular arrhythmias were suppressed by pacing at rates up to 120 beats per minute. In both cases, fluoroscopy was required for proper electrode placement although a successful attempt had been made to guide one electrode blindly into place by using the electrode tip as an intracavitary electrocardiographic lead.[2] Later, Heiman and Helwig[3] reported two similar cases wherein transvenous electrodes were guided fluoroscopically into the heart. In one of their patients pacing from the right atrium was successful in terminating the arrhythmias. In the other, pacing by means of an electrode in the right ventricle was continued for over six months.

In 1966, Schoonmaker and associates[4] described the successful treatment of a patient with recurrent serious arrhythmias presumed to be due to thioridazine (Mellaril). A unipolar pacemaker electrode was passed pervenously into the right ventricle and suppression of the arrhythmia was achieved by pacing the heart at a rate of 90. In a similar case reported in 1967 by Lew and March,[5] pacing at a rate of 90 through a bipolar electrode catheter in the right ventricle aborted repetitive ventricular arrhythmias thought to have been induced at least in part by digitalis excess.

Chardack and co-workers[7] mention a patient in whom rapid ventricular pacing for several days overcame drug-resistant ventricular tachyarrhythmias in the presence of intact A-V conduction. Chardack[8]

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has had further experience in suppressing serious ventricular arrhythmias in similar patients by the use of pacemaker wires left in place in the ventricle after cardiac operation or inserted by percutaneous puncture of the left ventricle. Harris and associates [1] have described the advantages of pacing at a rate faster than that of the intrinsic pacemaker in order to suppress ectopic activity after cardiac operation. For this purpose they have used thin wires inserted into the ventricle and/or atrium at the time of operation. Eraklis and colleagues[11] have also reported effective use of temporary pacing for refractory ventricular arrhythmias which developed after cardiac operation. In their patient who had undergone a mitral commissurotomy external pacing was first employed but, because of the discomfort produced by this method, an electrode catheter was introduced into the right atrium from the right external jugular vein. Effective right atrial pacing at a rate of 90 per minute suppressed the ectopic activity.

In addition to temporary pacing, there have been a few reports of permanent pacemakers that have been installed for the long term treatment of recurrent ventricular arrhythmias in the presence of normal A-V conduction.[18] Two recent reviews on pacing have also mentioned this method of treatment.[13]

In most cases where such dangerous drug-resistant arrhythmias occur, effective therapy must be undertaken quickly. Moving the patient to a fluoroscopy suite for catheter electrode placement may be both hazardous and impractical. In such cases, this difficulty can usually be met by using as a pacemaker electrode a Teflon-coated platinum-tipped stainless steel wire which is inserted percutaneously into a basilic, jugular, or femoral vein in a manner first described by Harris and associates[1] and by Kimball and Killip. In the absence of venous obstruction, these wires will usually follow the venous stream into the right atrium and frequently into the right ventricle as well. Electrocardiographic monitoring of the electrode provides intracardiac patterns which assume characteristic forms in the right atrium and right ventricle and usually permit accurate localization of the tip within the heart.[19] Pacing can then be instituted from either the right atrium or right ventricle by using this electrode in combination with an indifferent electrode sutured to the skin.

Two patients have recently been described in whom nearly fatal ventricular arrhythmias were abolished by pacing the heart with such a free-floating wire positioned in the right atrium.[20] These ventricular arrhythmias were refractory to drug therapy. In one of the patients, the arrhythmias recurred after temporary wire electrodes had been removed on two separate occasions. A permanent pervenous pacemaker was inserted with the electrode tip placed at the junction of right atrium and superior vena cava for what proved to be successful suppression of the arrhythmia.

In pacing with intact A-V conduction, either the right atrium or right ventricle can be used. However, there would appear to be several advantages to stimulating the heart from the right atrium. First, there is the preservation of cardiac output that occurs when a coordinated atrial contraction properly precedes ventricular systole.[22, 23] Second, there is less danger of the electrode itself generating further ventricular irritability when its tip lies in the right atrium rather than in the right ventricle, and third, the possible hazard of entrapment of the electrode in the trabeculae carnae or chordae tendineae of the right ventricle is avoided. In most cases the atrium can be satisfactorily paced unless atrial flutter or fibrillation are present. In one such case[24] atrial fibrillation was coincidentally converted while external countershock was being employed to terminate ventricular fibrillation, thus permitting successful capture of the right atrium. Satisfactory atrial pacing cannot always be achieved, as we found it impossible to stimulate the right atrium in one patient in whom this chamber was greatly enlarged. Furthermore, occasional problems also arise in directing, localizing, and

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maintaining the position of the small free floating wires. In such cases a stiffer bipolar transvenous pacing electrode can usually be guided under fluoroscopic control into the heart.

The likelihood that such ventricular arrhythmias could be suppressed by rapid pacing might have been predicted from the experience with pacemakers in A-V block. At faster heart rates diastole is shortened, thereby providing less opportunity for ectopic ventricular activity to arise. In addition, it is possible that other consequences of rapid pacing such as reduced diastolic volume, decreased stretch on Purkinje fibers,[7] and increased cardiac output with elevated coronary flow and hence relief of myocardial ischemia may all contribute to suppression of ectopic foci. However, it is difficult to invoke these factors exclusively at the rapid stimulation of over 100 beats per minute which have been found necessary to suppress irritable foci in some of the reported cases with normal A-V conduction. In diseased hearts, cardiac output may fall at these heart rates,[28,29] and furthermore any tachycardia is costly in terms of increased myocardial oxygen consumption. It is tempting then to ascribe the results of such pacing at least in part to a suppressive effect on the intrinsic ectopic foci which does not depend entirely on improved myocardial function.

In other settings, examples of depression of one pacemaker by another are frequently seen in circumstances where improvement of myocardial function cannot be considered the sole cause. Momentary slowing of the sinus node by an ectopic atrial beat is a common observation.[31] In addition, Langendorf and Pick[32] have demonstrated how periods of rapid ectopic activity may delay the emergence of escape foci after the tachycardia ends, leading to asystole and Adams-Stokes episodes. Experimental evidence supporting these clinical observations is also available.[33-35]

Physiological factors which may also play a role in the suppression of pacemakers by "overdriving" include (1) the release of acetylcholine and other autonomic mediators by the pacing stimulus[34] and (2) shifts in potassium concentrations in the intra- and extra-cellular milieu.[35] Of interest are observations that the amplitude of the action potentials of pacemaker cells is reduced and their threshold is raised as pacemakers are suppressed.[35] Evidence is also available to show that slight variations in the rate of recovery of excitability in neighboring ventricular tissues develops in the presence of premature beats[36] and with slowing of the heart rate.[37,38] Such momentary changes in potential between adjacent tissues may encourage the production of ectopic pacemakers. When several ventricular centers are released, asynchrony in fiber discharge develops and the progression toward ventricular fibrillation may follow.[39] Sufficiently rapid pacing, however, may prevent this deterioration from occurring by presumably preventing the development of injurious asynchrony in fiber discharge and recovery. Although "overdriving" may be a major factor in suppressing ectopic foci, it is of course possible that the rapidly paced heart merely captures the ectopic sites without really suppressing them. Proof for or against this concept is lacking.

The primary therapy of ventricular arrhythmias in the absence of A-V block is the use of myocardial depressant drugs such as quinidine, procainamide, lidocaine, diphenylhydantoin, and propranolol. However, drugs of this type usually administered to *depress* ectopic activity have been shown under some circumstances to *increase* paradoxically the ventricular arrhythmias.[39,40-42] When such is the case, rapid pacing may be life-saving. Furthermore, after adequate pacing has been established, these antiarrhythmic drugs may then be concomitantly employed with less risk and more efficacy should they be necessary. Such treatment of refractory ventricular arrhythmias by a combination of electrical pacing and propranolol has recently been reported by Cohen and associates.[11]

In most of the reported cases, conversion of the arrhythmias with countershock was necessary as an emergency measure at some time during the course of treatment. When digitalis intoxication is the cause of the uncontrolled ventricular ectopicity, as it has been in some cases, external countershock may be particularly hazard-

ous as it may further encourage the release of ectopic foci and exacerbate the irritability.[9] With digitalis-induced ventricular arrhythmias—either those spontaneously occurring or those generated by countershock—rapid atrial pacing would appear to be particularly useful. For if the heart can be successfully captured, pacing can be continued until the effect of the excessive digitalis has waned, at which point pacing may be stopped.

Thus, pacing to suppress arrhythmias can be considered a temporary expedient to tide the patient over a critical period until the irritability is diminished by the beneficial effects on myocardial function of the regular properly timed artificially induced rhythm or until factors causing the irritability are eliminated. In rare instances when long term pacing is required slower rates may prove adequate. In the permanent units that have been used, rates of 110, 100[11] and 90[12] were found to be satisfactory.

Dangers inherent in this method, however, should not be minimized. In particular, the hazard of precipitating fatal ventricular arrhythmias by way of electric currents carried to the heart over the pacemaker electrodes has been frequently emphasized.[11,9] It is vital that all electric equipment coming into contact with such patients be thoroughly grounded. The difficulties which may be expected should a parasystolic competitive rhythm develop are discussed in an editorial by Greenfield and Orgain. Under these circumstances, a pacemaker impulse may fall into the vulnerable phase of the T wave of the previous intrinsic beat. In this event, precipitation of ventricular fibrillation is a potential hazard. In the cases reported, however, increasing the rate of the pacemaker usually suppressed all ventricular irritability, thus decreasing such dangers.

Occasionally the pacing rates required to suppress ventricular irritability may be excessively rapid. In diseased hearts, these fast rates may themselves contribute to cardiac decompensation, although fortunately this has not yet been a problem in cases treated by us. However, it would appear advisable to pace the heart at the slowest rate commensurate with adequate suppression of ventricular irritability and to reduce the pacing rate as quickly as possible after life threatening irritability has been controlled.

The technique of rapid pacing, then, appears to have value in the treatment of recurrent ventricular arrhythmias refractory to the more usual pharmacologic measures. Atrial pacing, where applicable, has distinct advantages over ventricular pacing in those patients where A-V conduction is intact. Teflon-coated stainless steel wire electrodes are particularly useful and safe when bedside placement is required. The technique has been shown to be life-saving in several cases and its more frequent application where appropriate seems reasonable.

REFERENCES

1. Sowton, E., Leatham, A., and Carson, P.: The suppression of arrhythmias by artificial pacemaking, Lancet 2:1098, 1964.
2. Sowton, E.: Personal communication, 1966.
3. Heiman, D. F., and Helwig, J., Jr.: Suppression of ventricular arrhythmias by transvenous intracardiac pacing, J.A.M.A. 195:1150, 1966.
4. Helwig, J., Jr.: Personal communication, 1966.
5. Schoonmaker, F. W., Osteen, R. T., and Greenfield, J. C., Jr.: Thioridazine (Mellaril)-induced ventricular tachycardia controlled with an artificial pacemaker, Ann. Int. Med. 65:1076, 1966.
6. Lew, H. T., and March, H. W.: Control of recurrent ventricular fibrillation by transvenous pacing in the absence of heart block, Am. Heart J. [illegible]:794, 1967.
7. Chardack, W. M., Gage, A. A., Federico, A. J., Schimert, G., and Greatbatch, W.: The long term treatment of heart block, Progr. Cardiovas. Dis. 9:105, 1966.
8. Chardack, W. M.: Personal communication, 1966.
9. Harris, P. D., Singer, D. H., Malm, J. R., and Hoffman, B. F.: Electrodes for chronic cardiac implantation in man, Am. J. Cardiol. 19:132, 1967.
10. Harris, P. D., Singer, D. H., Malm, J. R., and Hoffman, B. F.: Chronically implanted cardiac electrodes for diagnostic, therapeutic, and investigational use in man, J. Thoracic & Cardiovas. Surg. 54:191, 1967.
11. Erakis, A. J., Green, W. T., Jr., and Watson, C. C.: Recurrent paroxysms of ventricular tachycardia following mitral valvuloplasty, Ann. Surg. 161:63, 1965.
12. McCallister, B. D., McGoon, D. C., and Connolly, D. C.: Paroxysmal ventricular tachycardia and fibrillation without complete heart block, Am. J. Cardiol. 18:898, 1966.
13. Swedberg, J., and Malm, A.: Pacemaker stimulation in ventricular paroxysmal tachycardia, Act. chir. scandinav. 128:610, 1964.

14. Cohen, L. S., Buccino, R. A., Morrow, A. C., and Braunwald, E.: Recurrent ventricular tachycardia and fibrillation treated with a combination of beta-adrenergic blockade and electrical pacing, Ann. Int. Med. 66:945, 1967.
15. Furman, S.: Fundamentals of cardiac pacing, Am. Heart J. 73:261, 1967.
16. Sowton, E.: Cardiac pacemakers and pacing, Mod. Conc. Cardiovas. Dis. 36:31, 1967.
17. Harris, C. W., Hurlburt, J. C., Floyd, W. L., and Orgain, E. S.: Percutaneous technic for cardiac pacing with a platinum-tipped electrode catheter, Am. J. Cardiol. 15:48, 1965.
18. Kimball, J. T., and Killip, T.: A simple bedside method for transvenous intracardiac pacing, Am. Heart J. 70:35, 1965.
19. Vogel, J. H. K., Tabari, K., Averill, K. H., and Blount, S. G.: A simple technique for identifying P waves in complex arrhythmias, Am. Heart J. 67:158, 1964.
20. Vetter, D. O., and Kelser, G. A., Jr.: The percutaneous intracavitary electrocardiogram in the diagnosis of arrhythmias, Ann. Int. Med. 62:706, 1965.
21. Kastor, J. A., DeSanctis, R. W., Harthorne, J. W., and Schwartz, G. H.: Transvenous atrial pacing in the treatment of refractory ventricular irritability, Ann. Int. Med. 66:939, 1967.
22. McIntosh, H. D., and Morris, J. J., Jr.: The hemodynamic consequences of arrhythmias, Progr. Cardiovas. Dis. 8:330, 1966.
23. Martin, R. H., and Cobb, L. A.: Observations on the effect of atrial systole in man, J. Lab. & Clin. Med. 68:224, 1966.
24. Samet, P., Castillo, C., and Bernstein, W. H.: Hemodynamic consequences of atrial and ventricular pacing in subjects with normal hearts, Am. J. Cardiol. 18:522, 1966.
25. Sowton, E.: Haemodynamic studies in patients with artificial pacemakers, Brit. Heart J. 26:737, 1964.
26. Benchimol, A., Ellis, J. G., and Dimond, E. G.: Hemodynamic consequences of atrial and ventricular pacing in patients with normal and abnormal hearts, Am. J. Med. 39:911, 1965.
26. Bevegard, S., Jonsson, B., Karlof, I., Lagergren, H., and Sowton, E.: Effect of changes in ventricular rate on cardiac output and central pressures at rest and during exercise in patients with artificial pacemakers, Cardiovas. Res. 1:21, 1967.
27. Pick, A., Langendorf, R., and Katz, L. N.: Depression of cardiac pacemakers by premature impulses, Am. Heart J. 41:49, 1951.
28. Langendorf, R., and Pick, A.: Causes and mechanisms of ventricular asystole in advanced A-V block, in Surawicz, B., and Pellegrino, E. D., ed.: Sudden cardiac death, New York, 1964, Grune & Stratton, Inc., p. 97.
29. Yormak, S. S., Killip, T., Levitt, B., and Roberts, J.: Depression of ventricular pacemaker by induced tachycardia, Clin. Res. 13:529, 1965.
30. Regel, S., and Stein, H.: The duration of post-pacing asystole in dogs with atrioventricular block, J. Thoracic & Cardiovas. Surg. 50:438, 1965.
31. Lu, H. H., Lange, G., and Brooks, C. McC.: Factors controlling pacemaker action in cells of the sinoatrial node, Circulation Res. 17:460, 1965.
32. Lange, G.: Action of driving stimuli from intrinsic and extrinsic sources on in situ cardiac pacemaker tissues, Circulation Res. 17:449, 1965.
33. Vassalle, M., Caress, D. L., Slovin, A. J., and Stuckey, J. H.: On the cause of ventricular asystole during vagal stimulation, Circulation Res. 20:228, 1967.
34. Vincenzi, F. F., and West, T. C.: Release of autonomic mediators in cardiac tissue by direct subthreshold electrical stimulation, J. Pharmacol. & Exper. Therap. 141:185, 1963.
35. Vassalle, M., Vagnini, F. J., Gourin, A., and Stuckey, J. H.: Suppression and initiation of idioventricular automaticity during vagal stimulation, Am. J. Physiol. 212:1, 1967.
36. Han, J., and Moe, G. K.: Nonuniform recovery of excitability in ventricular muscle, Circulation Res. 14:44, 1964.
37. Han, J., Millet, D., Chizzonitti, B., and Moe, G. K.: Temporal dispersion of recovery of excitability in atrium and ventricle as a function of heart rate, Am. Heart J. 71:481, 1966.
38. Han, J., DeTraglia, J., Millet, D., and Moe, G. K.: Incidence of ectopic beats as a function of basic rate in the ventricle, Am. Heart J. 72:632, 1966.
39. Watanabe, Y., and Dreifus, L. S.: Genesis of ventricular arrhythmias, in Cardiovascular Drug Therapy, New York, 1965, Grune & Stratton, Inc., p. 442.
40. Pick, A.: Manifestations of a vulnerable phase in the human heart, in Surawicz, B., and Pellegrino, E. D., ed.: Sudden cardiac death, New York, 1964, Grune & Stratton, Inc., p. 44.
41. Selzer, A., and Wray, H. W.: Quinidine syncope—paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias, Circulation 30:17, 1964.
42. Seaton, A.: Quinidine-induced paroxysmal ventricular fibrillation treated with propranolol, Brit. M. J. 1:1522, 1966.
43. Kleiger, R., and Lown, B.: Cardioversion and digitalis. II. Clinical studies, Circulation 33:878, 1966.
44. Burchell, H. B., and Sturm, R. E.: Electroshock hazards, Circulation 35:227, 1967.
45. Whalen, R. E., and Starmer, C. F.: Electric shock hazard in clinical cardiology, Mod. Concepts Cardiovas. Dis. 36:7, 1967.
46. Greenfield, J. C., and Orgain, E. S.: The control of ventricular tachyarrhythmias by internal cardiac pacing, Ann. Int. Med. 66:1017, 1967.

Incomplete differentiation of the cardiac valves

A report of 197 cases

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During our study of congenital heart anomalies, we have frequently encountered an irregular nodular formation of the semilunar and atrioventricular heart valves that we feel is of congenital origin (Figs. 1 to 4). These valvular lesions are often associated with other congenital cardiac lesions. We refer to these lesions as incomplete differentiation of the heart valves, a designation first used by Abbott in 1936 in referring to similar appearing valvular lesions. This seems an appropriate descriptive name from a histogenetic basis. Synonyms appearing in the literature and common usage to designate apparent analogous valvular lesions include myxomatosis,[12] myxoma, mucinous fetal endocardiosis, dysplasia of leaflet endocardium,[illegible] fibromyxoma,[illegible] fibromyxomatous hyperplasia,[illegible] congenital myxoma,[illegible] myxoid dysplasia, and hamartoma.[illegible] These lesions of the valves have been variously interpreted by different authors as a primary neoplasm,[illegible] the sequelae of an infectious process,[illegible] organized thrombi,[illegible] a manifestation of endocardial sclerosis,[illegible] or a congenital maldevelopment.[illegible]

This lesion of the heart valves, in our experience, appears to be more common than the literature indicates. Textbooks discussing congenital heart disease[illegible] note these valvular lesions, but reference to them is limited usually to a comment on the grossly deformed stenotic or insufficient valve with its peculiar nodular, warty, or tumor-like appearance. We have also noted a tendency of the contributing pathologists either to overlook or to ignore these valvular lesions in their assessment of some of the congenital heart lesions sent to the Armed Forces Institute of Pathology.

This paper presents a gross and microscopic description of the valvular lesion, statistical data, and a discussion of the histogenesis and pathophysiologic features based on 197 cases on file at the Armed Forces Institute of Pathology.

Historically, Parrot[illegible] in 1874 described gross fibrouslike nodules present on cardiac valves of infants that he considered as organized hemorrhages. Ariel in 1930 and Abrahamer[1] in 1931 reported tumor-like lesions on the atrioventricular valves of newborns, considered by Ariel to be of congenital origin. Stohr[illegible] in 1934 presented the cases of two newborn infants with warty growths on the aortic valves in association with endocardial sclerosis. He considered the two entities to be of in

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flammatory origin. Eck[11] in 1939 described tumorous lesions of the aortic and pulmonary valves in a premature newborn of 7 months gestation that he termed a true myxoma. A review of the literature on primary heart tumors by Jacobsson[illegible] in 1943 included his two personal cases of infants with verrucous formations of the aortic valve that he termed myxofibromas but considered to be of possible developmental origin. Craig[8] in an extensive study of congenital endocardial sclerosis described thickened tumorous formations on the valves occurring with and without endocardial sclerosis, both of which he considered developmental abnormalities. Additional cases presenting cardiac valvular lesions in infants, children, and young adults that appear to us to be consistent with the lesion we are describing have been reported.[illegible] The authors' opinion as to the genesis of the lesion varied, including the suggestions of neoplasia, inflammation, or congenital maldevelopment. An additional recently published paper by Fadell and Graziano[illegible] concerned two infants with this lesion involving the aortic valve and associated with extensive myocardial necrosis. These two cases are included in this study. The association of myocardial necrosis with the aortic valvular lesion will be discussed later.

Materials and methods

The source of material for our study is the collection of approximately 4,500 gross hearts with congenital anomalies on file at the Armed Forces Institute of Pathology. Contributors to this collection included military, Veterans Administration, and civilian hospitals in the United States and abroad. Of these 4,500 hearts, the lesion in 19[illegible] involved either a single valve or multiple heart valves. All the involved hearts were accompanied by clinical summaries and autopsy protocols. In 184 cases, histologic slides of the myocardium and other body organs were available. In a representative selected 50 cases, histologic slides of the valve lesions were prepared; in the remaining cases, the hearts were preserved intact for anatomic study.

The sections from the valvular lesions were stained with Mayer's hematoxylin and eosin, the acid mucopolysaccharide stain of Mowry, Hart's elastica, and Movat's pentachrome stain. In cases with ischemic changes of the myocardium Masson's trichrome stain was additionally employed.

For a comparative study, in an attempt to explain the histogenesis of these valvular lesions, the normal hearts of 30 grossly normal fetuses in the eighth to twelfth week of intrauterine development were examined. Sections from the semilunar and atrioventricular valves of these hearts were stained by the same methods indicated above.

Results

Gross findings. The lesions are most dramatic in the fresh state, in which they appear as moist, glistening, translucent, varying-sized nodular swellings on the affected valve or cusp (Fig. 1). Manipulation reveals lesions to be firmly incorporated into the valve substance; they are not friable, nor can they be detached. With fixation, the lesion contracts, loses its glistening edematous appearance, and becomes opaque and leathery. One or all cusps or leaflets of the valves can be involved. The lesion may be localized at any point from the free edge to the insertion of the valve, or the entire valve cusp or leaflet may be replaced by the nodular mass or masses. The lesion usually produces an irregular thickening and distortion of the valve cusp or leaflet that may either encroach upon the valve lumen, causing stenosis (Fig. 3), or retract, producing an insufficiency (Fig. 4). Nodules have been noted arising on the chordae tendineae or on rare occasions may hang free in the heart cavity (Fig. 2). Blood cysts may be associated with or incorporated into the lesion, especially in the cases of neonatal death (Fig. 2). Malformed valves such as the common atrioventricular valves, common truncal valves, and stenosed or bicuspid semilunar valves are frequently affected (Figs. 1 and 2).

Microscopic findings. The luminal surface of the affected valve is covered by an intact, normal appearing endothelial layer, while the lesion proper consists of an avascular, fibrillar, eosinophilic, loosely arranged myxomatous stroma in which there is a variable distribution and arrange-

Fig. 1 Photograph of the truncal valve (unfixed) from a case of persistent truncus arteriosus in day-old, full-term male infant showing the glistening translucent nodular deformities of the cusps. (AFIP 60-10508-1.)

Fig. 2 Photograph of the atrioventricular valve of 5-day-old, full-term male infant, viewed from the right side, in case of persistent common trioventricular canal, complete type. Note the nodular valve lesions, arising in some instances from the chordae tendineae, and the associated blood cysts focally incorporated the valve lesions. (AFIP 1198390.)

Fig. 3 Aortic valve and interventricular septal defect in the unfixed heart of 6-month-old female infant. Note the irregular glistening nodular thickenings of the aortic cusps, which produced a prominent stenosis of the aortic valvular orifice. (AFIP 61 9565.)

Fig. 4 Right atrioventricular valve (formalin-fixed) of full-term newborn male infant with mitral valve atresia. Note that in addition to the nodular deformity of the valve leaflets, there is nodular mass of tissue hanging free in the ventricular cavity (AFIP 56-22534.)

ment of small spindle cells resembling fibroblasts (Fig. 5). These spindle cells have a small elongated oval nucleus with a nucleolus usually poorly defined and an irregularly distributed fine granular nuclear chromatin. A thin straplike band of eosinophilic cytoplasm surrounds the nucleus. Focally irregular small islands of collagenous connective tissue are seen in the myxomatous stroma. On occasion endothelium-lined blood-filled cysts are incorporated into the lesion proper. In none of the sections of the valvular lesions studied was there acute or chronic inflammation, necrosis, or evidence of old or recent hemorrhage.

Special stains reveal an abundance of acid mucopolysaccharide throughout the valvular lesions. Elastic tissue is absent in the lesion proper. A thin zone of elastic

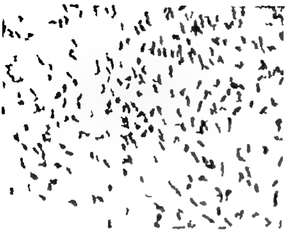

Fig. 5. Photomicrograph of representative area of the valve lesions showing the characteristic stroma with its irregularity in arrangement of otherwise uniform spindle cells resembling fibroblasts. (Mayer hematoxylin and eosin ×230. AFIP 66-9299.)

Fig. 6. Gross heart of 3-week-old full-term male infant showing the gross nodularity of the aortic valve and the prominent discoloration of the ventricular wall at the site of the focal myocardial necrosis. (AFIP 52-4228.)

tissue was occasionally noted limited to the subendothelial area on the surface of the lesion and at the juncture of the lesion with the adjacent normal valve or endocardium.

Clinical findings. There were 110 male and 87 female patients in the series—a ratio in keeping with the predominance of men in over-all congenital heart disease. Further classification revealed 171 Caucasians, 12 Negroes, 3 Mongolians, 4 Malaysians, 1 Eurasian and 1 American Indian; in five cases the race was not recorded. The racial findings appear to have little significance because the majority of cases are from military families with no definite established geographic or racial pattern.

There was a definite history of first trimester maternal rubella infection recorded in three cases. This incidence is identical to the 1 to 2 per cent reported occurrence of first trimester maternal rubella recorded in over-all congenital heart disease.[27]

The lesion involved all heart valves either singly or in various combinations of multiple valves (Table I). The predominance of involvement of the aortic valve, though not readily explainable, should be emphasized because of the frequent association of myocardial necrosis with the lesions of the aortic valve (Fig. 6). This relationship will be further discussed.

The lesion is of the younger age group, as is evident by the ages of death recorded in Table II. Since the majority of cases had additional serious congenital cardiac anomalies, the ages of death correspond favorably with the mortality age of over-all congenital heart disease,[27] except for the prominent absence of cases in our series beyond the eighth year of life. The reason for this is not readily understood. The published cases showed the same age group deficiency. Perhaps the combination of the valvular deformity and the accompanying congenital cardiac defect may account for the shortened life span.

Tabulation of the primary congenital cardiac defect in each case with the single or multiple valves involved with the lesion is given in Table III. Attention is directed, however, to the 35 cases in which the valve lesion was considered the primary defect, which emphasizes the significance of this valvular lesion. Of these 35 cases, 18 were under three weeks of age, 14 were between one and seven months, and 3 were three, five and seven years, respectively, at death. Other congenital cardiac lesions noted in these 35 cases, but considered to be of lesser physiologic importance in the cardiac deformity, were interatrial septal defect (small)–12 cases, interventricular septal defect (small)–6 cases, endocardial sclerosis–5 cases, bicuspid aortic valve–2 cases, single coronary ostia–1 case, dextro-

Table I. Specific heart valves involved in 197 cases of incomplete differentiation of heart valve

*Valve(s) involved**	*No. of cases*	*Approx percentage*
AV only	55	28.0
PV only	30	15.0
MV only	10	5.0
TV only	49	25.0
AV and PV	2	1.0
AV and MV	6	3.0
AV and TV	4	2.0
PV and MV	1	0.5
PV and TV	6	3.0
MV and TV	13	7.0
AV, PV, and MV	1	0.5
AV, PV, and TV	3	1.5
PV, MV, and TV	2	1.0
AV, PV, MV, and TV	1	0.5
Common truncus V	6	3.0
Common A-V	8	4.0

Abbreviations: AV, Aortic valve; PV, pulmonic valve; MV, mitral valve; TV, tricuspid valve; A-V, atrioventricular; A-V V, atrioventricular valve; IVSD, interventricular septal defect; End., endocardial; PFO, patent foramen ovale; PDA, patent ductus arteriosus; Trans. G.V., transposition of the great vessels; IASD, interatrial septal defect; C. Art., coronary artery.

Table II. Ages at death in cases with incomplete differentiation of heart valves

Age at death	*No. of cases*	*Approx percentage*
Stillborn	3	2.0
24 hr	18	9.0
24 hr. to 3 mo.	97	49.0
4 to 6 mo.	33	17.0
7 to 9 mo.	12	6.0
10 to 12 mo.	4	2.0
2nd yr	12	6.0
3rd yr	5	3.0
4th yr	3	1.5
5th yr	3	1.5
6th yr	4	2.0
7th yr	1	0.5
8th yr	1	0.5
19th yr	1	0.5

*See Table I for abbreviations.

cardia–1 case, pulmonary stenosis–1 case, and patent ductus arteriosus–1 case. (In 10 cases, all under two months of age, there was a patent ductus arteriosus which we arbitrarily accepted as being within the limits of normal.) A total of 11 cases revealed no other congenital cardiac deformity except the valve lesion. The table also shows that the most common primary congenital defect accompanying the valvular lesion is the interventricular septal defect, which is also the most common congenital heart defect reported in over-all congenital heart disease surveys.[13-20] Save for this one exception, the valvular lesion in question does not necessarily parallel the more frequently occurring congenital heart defects, but tends to occur more commonly in those hearts with primary congenital valvular anomalies.

Of the 73 cases involving the aortic valve occurring either singly or in combination with lesions of other valves, 41 cases revealed evidence of myocardial ischemia (Figs. 6, 7, and 8) with histologic changes including myocytolysis, calcification, diffuse fibrosis, and acute necrosis. This finding is in contrast to that of Brown, who felt that myocardial degenerative changes were infrequent in any congenital cardiac anomaly. Of these 41 cases, 3 had undergone previous operation. Of the 124 cases with other than the aortic valve lesion, 29 showed histologic evidence of relatively minor myocardial ischemic change. Nine of this latter group had undergone previous operation.

Discussion

The terminology "incomplete differentiation of the heart valves" employed by Abbott[1] indicated that she felt that the lesion is a result of a failure of embryonic valvular tissue to mature normally.

To demonstrate the similarity of this valve lesion to immature embryonic valves, the semilunar and atrioventricular cardiac valves of 8- to 12-week-old fetuses were employed for a histologic and histochemical comparison. We selected valves from this age group because at this period of intrauterine development the valves are recognized grossly but are still composed of poorly differentiated cardiac mesenchyme as was pointed out by Shaner[22] and Licata.[23] A histologic comparison between the normal cardiac valve of the 8- to 12-week-old fetus

*Table III. Specific valvular involvement with tumor-like differentiation in 19 cases as related to presence of primary congenital anomaly**

Primary congenital anomaly present	AV	PV	MV	TV	AV PV	AV TV	AV MV	PV TV	PV MV	MV TV	AV PV TV	AV PV MV	PV MV TV	AV PV MV TV	Common truncus valve	Common AV valve
IVSD		11		19				4		4	1	1				
Incomp. d.c. (alone)	11	6	3	6									1			
AV stenosis	16	1														
AV atresia													1			
PV stenosis		5	1													
PV atresia	4			1												
Truncus arteriosus															9	
End. sclerosis	10	1	8													
AV communis	1															8
MV stenosis			1	1												
MV atresia	1															
PFO					1											
PDA			1	1												
Trans. G V	1	4		9												
IASD		1														
TV atresia	1	1	1													
Coarc. aorta	1															
C art. anomaly														1		
Cor triatriatum				1												

*See Table I for abbreviations.

(Fig. 9) and a section from the incompletely differentiated valve lesion (Fig. 5) shows identical structure. Histochemical studies reveal an abundance of acid mucopolysaccharide in both the control and the valve lesion but absence of elastic tissue. These findings support the concept that the valvular lesion is the result of a failure of full maturation on the part of the developing valve. While some stimulus for maturation appears to have been present since the valve apparently developed to a limited extent, the stimulus appears to have lacked sufficient force to bring the valve to complete maturation. Hence the tumor-like appearance of the incompletely differentiated valve lesion appears to represent an early embryonic stage of development.

The possibility that this lesion of the valve may be the result of a hemodynamic disturbance resulting from associated congenital heart defects was considered, but the occurrence of the valve lesion in only 5 per cent of the Armed Forces Institute of Pathology (AFIP) collection of congenital deformed hearts, plus the occasional occurrence of the valve lesion in the absence of other congenital cardiac defects, would indicate that this is not a likely cause.

From the opinions expressed in other publications, it would seem that the lesion of the valve is considered by some as a primary neoplasm, that is, a myxoma. We do not feel so, however. Histologically it lacks many of the features of the latter lesion, such as vascularity, hemorrhage, hemosiderin deposits, inflammatory cell infiltrates, or elastic tissue content. In addition, in contrast to the myxoma, which is a tumor primarily of the adult age group, the valvular lesion in question occurs mainly in infancy and early childhood. Also, in contrast to the discussed lesion, which is primarily valvular in origin, the myxoma arises chiefly from the interatrial septum of the left atrium, usually in the region of the valve of the foramen ovale and

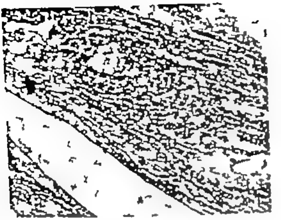

Fig. 7. Photomicrograph of an area of the left ventricular myocardium from 5-week-old, full-term male infant, showing focal acute myocardial necrosis. Marked nodular deformity of the aortic valve was present in this case. (Mayer hematoxylin and eosin. ×80. AFIP 66-9052.)

Fig. 8. Photomicrograph of an area of the left ventricle of 6-week-old full-term male infant with incomplete differentiation of the aortic valve. The myocardium shows an area of the coagulation type of necrosis surrounded by focal areas of fibrosis, with calcification and mixed inflammatory infiltration. (Mayer hematoxylin and eosin. ×25. AFIP 66-9050.)

rarely from the heart valves. Ventricular and valvular myxomas, though they do occur, are rare. Tumor embolization and infiltrative tendencies, which may occur with the myxoma, were not recognized with this entity. Congenital cardiac anomalies may occur but are infrequently associated with the true myxomas.

The association of endocardial sclerosis with this valvular lesion has been described.[1,22,17,3,39,27,49] Though a definite cause of endocardial sclerosis has not been proved, some authors[24,30,35,36] feel that the endocardial sclerosis and the valvular lesions are related disease processes. Kelly and Anderson[34,36] described the histologic pattern of the valvular lesion in their cases as being identical to that of endocardial sclerosis; our findings revealed them to be distinctly different, however. Others have felt that the valvular lesions probably represent an extension of the endocardial sclerosis.[15] Although it is difficult to explain this association (of 109 cases of endocardial sclerosis in the AFIP heart collection, 34 revealed the valvular lesion—Table IV), we do not feel that they are necessarily the same disease entity, since the valvular lesion can occur in the absence of endocardial sclerosis.

In addition, there does not seem to be any histologic similarity between the compact collagenous connective tissue, with

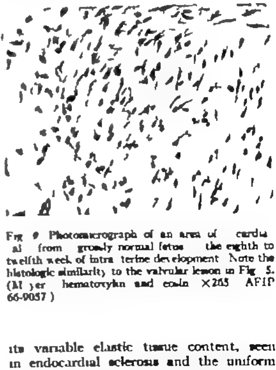

Fig. 9. Photomicrograph of an area of cardiac ... al from grossly normal fetus ... the eighth to twelfth week of intra-uterine development. Note the histologic similarity to the valvular lesion in Fig. 5. (Mayer hematoxylin and eosin. ×265. AFIP 66-9057.)

its variable elastic tissue content, seen in endocardial sclerosis and the uniform nonelastic embryonal myxomatous tissue of the valvular lesion.

That the valvular lesions are not extensions of endocardial sclerosis is made clear in the 163 cases in our study that did not show endocardial sclerosis on gross or histologic examination. It also is of

26. Klein, E. C., and Kharr, M. M.: Of congenital fibromyxomatous hyperplasia of the heart valves, Arch. Path. 26:53, 1964.
27. Licata, R. H.: Human embryonic heart in ninth week, Am. J. Anat. 94:73, 1954.
28. MacLean, L. D., Culligan, J. A., and Kane, D. J.: Subaortic stenosis due to accessory tissue on the mitral valve, J. Thoracic & Cardiovas. Surg. 45:382, 1963.
29. Maxwell, C. J., and Young, W. P.: Isolated stenosis (due to fibroelastosis) in infant of three months. Case treated surgically, Am. Heart J. 48:8?, 1954.
30. Parrot, M. H.: Sur les hemato nodules cardiaques chez les jeunes enfants, Arch. Physiol. Norm. Path. 6:538, 1874.
31. Plachta, A., and Speer, F. D.: Eisenmenger's complex in association with congenital tricuspid endocarditis (fetal). Review of literature and report of case, J. Pediat. 42:325, 1953.
32. Potter, E. L.: Pathology of the fetus and the infant, Chicago, 1961, Yearbook Medical Publishers, Inc.
33. Prichard, R. W.: Tumors of the heart, review of subject and report of 150 cases, Arch. Path. (Chicago) 51:98, 1951.
34. Prior, J. T.: Mitral valve, congenital anomalies associated with long survival, Am. Heart J. 46:649, 1953.
35. Prior, J. T., and Wyatt, T. C.: Endocardial fibroelastosis. A study of eight cases, Am. J. Path. 26:269, 1950.
36. Reddy, P. J., Rao, S. P. T., Venkaiah, K. R., Gupta, K. G., Devi, P. S., and Naidu, N. B.: Congenital myxoma of the heart, Indian J. Pediat. 23:210, 1956.
37. Rosahn, P. P.: Endocardial fibroelastosis, old and new concept, Bull. New York Acad. Med. 31:453, 1955.
38. Shaner, R. F.: Abnormal pulmonary and aortic semilunar valves in embryos, Anat. Rec. 11?:?5, 1963.
39. Sherman, F. E.: An atlas of congenital heart disease, Philadelphia, 1963, Lea & Febiger Publishers.
40. Stohr, C.: Malformation of the heart of the newborn. Congenital lesions suggestive of an inflammatory origin, Arch. Path. (Chicago) 1:311, 1934.
41. Taussig, H. E.: Congenital malformations of the heart, vol. 2, Cambridge, Mass., 1960, Harvard University Press.
42. Wharton, C. M.: Primary malignant tumors of the heart, Cancer 2:245, 1949.

Norepinephrine- and heparin induced changes in plasma free fatty acids: A comparison between patients with ischemic heart disease and normal young adults

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Abnormalities in the metabolism of saturated fatty acids have been suggested as having possible etiologic significance in atherosclerosis. Therefore it would appear worthwhile to determine whether the lipolytic effects of norepinephrine (NE) and of heparin would reveal changes in plasma free fatty acids (FFA) in atherosclerotic patients which might differ from those in normal subjects.

The major obstacle in designing such a study is the impossibility, on clinical grounds, of selecting with certainty age matched nonatherosclerotic subjects as controls. Common experience has been that some apparently healthy persons may have more extensive vascular disease than subjects who have sustained a myocardial infarction. It is impractical and unethical to subject normal persons to angiographic studies in order to exclude the presence of vascular disease. This obstacle cannot be circumvented by selecting as controls younger persons who are more likely to be free of atherosclerosis. Failure to find a difference between such controls and atherosclerotic individuals could be due to the possibility that a metabolic abnormality might be present for years before it gives rise to atherosclerosis. On the other hand, any differences found between such two groups could be due to the "aging" process, to atherosclerosis, or to other more subtle factors. Nonetheless, significant differences between two such groups would lead one to search diligently for methods to distinguish the specific changes of aging from those of atherosclerosis. It is for this reason that we sought to compare the findings in patients with ischemic heart disease, a clear-cut landmark of the presence of atherosclerosis, to those in normal young subjects. We did find differences which we think may be important.

Material and methods

Six healthy male medical student volunteers (ages 25 to 27) and six patients (5 men and 1 woman) with known clinical coronary artery disease and past myo-

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cardial infarction were studied. The ages of the coronary patients varied from 48 to 68 years (average 58) and all had sustained myocardial infarction from 4 months to 11 years prior to the study. All of the patients were hospitalized for investigation of complaints of chest pain with no evidence of recent myocardial infarction. None of the patients was diabetic and all had blood pressures within normal limits. All patients were on regulation house diets with at least 150 to 200 grams of carbohydrates daily.

Five of the six coronary patients and all of the normal control subjects were within the normal weight range for their height according to the present life insurance standards. One patient was 3 pounds over the accepted standard but this amounted to less than 2 per cent of normal body weight. None of the patients had been on a restricted diet prior to hospitalization except that some of them had felt that they might have had somewhat less butter and eggs than they had taken in previous years. The house diet on which they were maintained in the hospital had no restrictions and contained approximately 2,000 calories. They were on this diet for approximately seven to ten days prior to the studies. All patients were ambulatory. None of the subjects acting as controls was on a restricted diet. Their diet may have differed from that of the patients only with respect to the amount of butter and eggs eaten. Even this is questionable because all control subjects were either medical students or technicians who were acutely aware of the present prevailing concepts of the causes of atherosclerosis. The patients' heights were 5 ft. 6 in., 5 ft. 1 in., 5 ft. 6 in., 5 ft. 11½ in., 5 ft. 6 in., and 5 ft. 9½ in., and their weights respectively 130 pounds, 108, 140, 167, 140, and 175 pounds. The heights of the control subjects were 5 ft. 6 in., 5 ft. 7 in., 6 ft., 6 ft. 3 in., 6 ft. 1 in., and 6 ft. 4 in., and their weights respectively were 140 pounds, 145, 165, 195, 172, 175, and 172 pounds. Each patient and each subject for control were told the nature of the experiment and its possible adverse effects. They were told to signal the physician immediately should discomfort or untoward symptoms develop. Extensive experience with the experimental use of NE in subjects with valvular heart disease[1] has shown that the hypertensive and arrhythmic effects of NE usually disappear within two minutes after the infusion is stopped. No undesirable permanent effects have been detected after its use in more than 200 subjects with valvular heart disease. These patients were not told which infusion was being used nor when it was started, and for this reason a 30 minute baseline period was used while an intravenous saline infusion was given slowly to allow any anxiety and apprehension to be minimized.

All studies were done after an overnight fast. Hospital patients were transported to the area for study by stretcher. Volunteer controls were asked to come to the hospital early in the morning and both groups were allowed to rest quietly or sleep for one hour in test surroundings. Smoking was prohibited after 6:00 P.M. the preceding evening.

After the rest period, a slow intravenous infusion of saline was allowed to run slowly in an arm vein for 30 minutes to achieve a basal level in case the stimulating effect of venipuncture had caused any transient rise in FFA. Samples for FFA were drawn before and after, and triglycerides (TG) after this saline infusion. On the days when sodium heparin (Lipo-Hepin, Riker) was studied, 100 mg. was injected intravenously through the tubing without the patients' knowledge. Successive samples of venous blood were drawn from a vein on the other arm for FFA determinations at 5, 10, 30, and 60 minutes following the injections. When NE (Levophed, Winthrop) was used, a similar procedure was followed. NE was infused from a separate bottle through the same tubing at a rate of 0.2 μg per kilogram per minute for 15 minutes and samples drawn before infusion was begun, 10 minutes after it was begun, and five minutes after it was discontinued. Klein and his co-workers[2] have shown the FFA peak after a 15 minute NE infusion to occur at 20 minutes. Blood pressures and pulse rates were monitored frequently during both heparin and NE studies so as to make both procedures as similar as possible to the patient. In order to minimize the possible effect of endogenous catecholamines as causing changes during

the heparin study a further method of testing was designed whereby the NE and heparin studies as described above were done successively on the same day the heparin given five minutes after NE infusion was stopped and samples drawn at 5 10 25 and 40 minutes after heparin

All samples were drawn into oxalated tubes, immediately placed in ice, and transported to an adjoining laboratory where the plasma was separated by centrifuging for 10 minutes at 4 000 g at 4 C FFA in the plasma were determined by a modification of Dole s method described by Sunderman and Sunderman[3] for FFA evaluation in serum the applicability of which has been reported previously The individual FFA were determined by a method described by Soloff and Schwartz. A standard fatty acid (FA) mixture of purified FA s obtained from the Hormel Institute yielded an analysis well within the limits suggested for major and minor components. TG determinations were measured on samples drawn after basal level was reached by the method of Jover

Results

The average rise in blood pressure after NE infusion for the coronary patients was 63/20 mm Hg systolic increases ranging from 40 to 90 mm Hg and diastolic increases from 6 to 42 mm. Hg The corresponding changes in controls were average increase 48/29 mm Hg systolic increases ranging from 28 to 88 mm. Hg and diastolic from 10 to 40 mm Hg

The average resting pulse in coronary patients was 70 per minute and the average fall in pulse rate of 7 per minute. In controls, average pulse was 63 per minute with an average fall of 14 per minute.

Mild transient substernal chest discomfort was precipitated in two coronary patients by the infusion The infusion was stopped for 30 seconds in one and one minute in another the pain disappeared and did not recur when the infusion was begun again. The infusion was allowed to run for an additional 30 seconds and one minute respectively at the end of the 15 minute period. In all patients and controls, the blood pressure began to decrease quickly immediately after the infusion was stopped and had returned to basal levels within 3 to 5 minutes. A transient rise in the pulse rate was seen in three of the control patients for 15 to 30 minutes after the infusion was stopped The blood pressure in these patients remained the same. There were no changes in ECG taken after completion of the procedure when compared to previous tracings for each patient.

Heparin injected in control patients did not lead to any changes in pulse rate or blood pressure. In the coronary group however there was a rise in pressure during the procedure in three patients. Two of these had transient rises of 18/6 mm. Hg with no change in pulse rate The other patient s pressure rose from 124/70 to 184/100 and the patient complained of mild substernal distress. Interestingly this patient tolerated NE infusion quite well without symptoms and with a rise of only 54/6 mm Hg blood pressure.

The fasting TG were elevated in four of six coronary patients and only minimally elevated in one normal (Table I) There was no consistent correlation between the fasting levels of plasma TG and the rise in FFA after NE or heparin.

The changes in total and individual FFA both in terms of absolute changes as well

Table I Comparison of fasting TG with increases of FFA after NE, heparin and the two in succession

Subject	TG (mg %)	Increases in FFA		mEq per liter
		NE	Hepar	NE-Heparin
Normal				
1	70	595	318	110
2	90	484	169	127
3	125	918	581	274
4	133	525	347	280
5	139	733	235	705
6	155	444	387	276
Coronary				
1	73	318	138	180
2	125	498	195	529
3	167	526	624	568
4	261	306	332	338
5	208	346	498	455
6	150	332	595	692

Table II. Mean increases in FFA (mEq. per liter) at 10 and 20 minutes after NE

	10 minutes			20 minutes		
	Normal	*Coronary*	*N vs. C**	*Normal*	*Coronary*	*N vs. C*
C 14 0	10.8 (0.01)	3.3	0	19.8 (0.01)	10.2 (0.01)	0.05
C 16 0	63 (0.01)	52 (0.05)	0	171 (0.01)	112 (0.01)	0.05
C 16 1	15 (0.01)	10	0	33 (0.01)	20 (0.01)	0.05
C 18 0	13 (0.05)	12	0	41 (0.01)	29 (0.01)	0.05
C 18 1	100 (0.01)	80 (0.05)	0	256 (0.01)	171 (0.01)	0.05
C 18 2	39 (0.01)	19	0	92 (0.01)	48 (0.01)	0.01
Total	240 (0.01)†	173 (0.05)	0	617 (0.01)	383 (0.01)	0.05

*N vs. C, Statistical comparison between normal and coronary subjects.
†Statistical significance of changes when each group compared to the baseline are enclosed in parentheses.

Table III. Mean changes in percentages of the total accounted for by each acid 10 and 20 minutes after NE

	10 minutes			20 minutes		
	Normal	*Coronary*	*N vs. C*	*Normal*	*Coronary*	*N vs. C*
C 14 0	0.73 (0.05)	−0.20	0	0.38	−0.10	0
C 16 0	−0.52	0.08	0	0.12	−0.27	0
C 16 1	1.21 (0.05)	0.75	0	1.40 (0.05)	0.78	0
C 18 0	−3.80 (0.01)	−2.17 (0.05)	0	−5.42 (0.01)	−3.48 (0.01)	0
C 18 1	4.98 (0.01)	4.27 (0.05)	0	8.48 (0.01)	6.46 (0.01)	0
C 18 2	−0.17	−0.85	0	−1.38	−0.70	0

as changes in percentage of the total for the individual FA for each infusion were subjected to statistical analysis and the principle findings given below. Individual FFA determined were C 14:0 (myristic), C 16:0 (palmitic), C 16:1 (palmitoleic), C 18:0 (stearic), C 18:1 (oleic), C 18:2 (linoleic), and C 20:4 (arachidonic). Levels of C 20:4 were quite low in comparison with other individual acids and significant changes thus difficult to evaluate. For this reason, subsequent findings below do not include this acid.

After 10 minutes' infusion of NE (Table II), there were significant increases in both total and individual FFA in normal subjects when compared to the baseline controls. Although some significant increases occurred in the coronary group, they did not appear to behave in such a clear-cut fashion as in the normal. Twenty minutes after infusion was begun, the total FFA, as well as all individual acids, had increased significantly more in the normal group than the coronary.

When the data were analyzed in the light of changes in percentages of individual FFA to the totals, that is, changes in FFA patterns after NE (Table III), both normal and coronary groups showed a significant decrease in the percentage of C 18:0 and an increased percentage of C 18:1 at both 10 and 20 minutes. For the normal group, NE seemed to produce a significant increase in percentage of both C 16:1 and C 14:0—an effect not noted in the coronary group, which actually showed a decrease in C 14:0. Although these differences were not

Table IV Comparison of mean change in FFA (mEq per liter) 5 and 10 minutes after heparin between normal and coronary subjects and comparison in the decrease of FFA from 10 to 60 minutes between these groups

	5 minutes			*10 minutes*			*60 minutes*		
	Normal	*Coronary*	*N vs. C*	*Normal*	*Coronary*	*N vs. C*	*Normal*	*Coronary*	*N vs. C*
C 14 0	7.5 (0.05)	7.8 (0.05)	0	8.3 (0.05)	5.8 (0.05)	0	5.3 (0.05)	− 2.8	0
C 16 0	59 (0.01)	90 (0.01)	0	94 (0 01)	115 (0 01)	0	− 57 (0.05)	−19	0
C 16 1	9 (0 01)	18 (0.01)	0.05	14 (0.05)	23 (0.05)	0	− 9	− 9	0
C 18 0	12 (0 05)	9 (0.05)	0	17 (0.05)	16 (0.05)	0	− 9	6	0 05
C 18 1	76 (0.01)	125 (0.01)	0	126 (0.01)	170 (0 01)	0	− 71	−44	0
C 18 2	36 (0.01)	39 (0.01)	0	54 (0.01)	57 (0.01)	0	33 (0.05)	−19	0
Total	201 (0 01)	287 (0.01)	0	318 (0.01)	388 (0.01)	0	−184 (0 05)	−88	0

Table V Mean changes in percentage accounted for by each acid 5 and 10 minutes after heparin normal vs coronary

	5 minutes			*10 minutes*		
	Normal	*Coronary*	*N vs. C*	*Normal*	*Coronary*	*N vs. C*
C 14 0	0.37	−0 03	0	0.17	−0.37 (0.01)	0
C 16 0	0.38	0.68 (0.05)	0	0.83	0.22	0
C 16 1	0.33	1.32 (0.01)	0.01	0.28	1 45 (0.01)	0 05
C 18 0	−4.32 (0.05)	−4.23 (0 01)	0	−5.83 (0.01)	−4.63 (0 01)	0
C 18 1	3.98 (0.05)	4.10 (0.01)	0	5 73 (0.05)	4 90 (0 05)	0
C 18 2	0.58	−0.33	0	0.60	0 10	0

statistically significant between the normal and coronary groups, there was the suggestion that C 16 1 increased substantially less in the coronary group

Heparin induced significant changes in both coronary and normal groups for both total FFA as well as all individual acids (Table IV) The only acid that differed significantly between the groups was C 16 1 which showed a significantly greater increase in the coronary group than in the normal.

In terms of percentage changes of individual FFA to the total heparin produced the same significant changes in the same two acids, C 18 0 and C 18 1 as NE C 18:0 decreased significantly and C 18 1 increased significantly in both groups (Table V) In addition the coronary group also showed a significant increase in percentages of C 16:0 and C 16 1 and a significant decrease in C 14 0, changes not noted in the normal. This increased percentage of C 16 1 was statistically significant when comparing the two groups both at 5 and 10 minutes

In both groups, the FFA tended to begin to decrease 10 minutes after heparin was given and by 60 minutes were much closer to the control stat for normals. This decrease from 10 minutes to 60 minutes was significant for the t tal and most of the individual FFA in the normals (Table IV) However the total and individual acids in the coronary group did not decrease significantly n this time period although the statistical comparison was only significant between the two groups for C 18 0 which

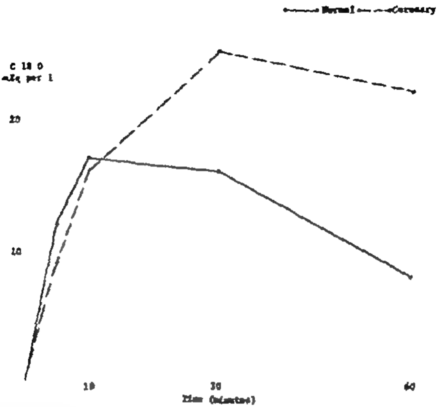

Fig. 1. Mean changes of stearic acid (C 18:0) from the baseline after heparin injection in coronary and normal subjects. Note similarity of increment up to 10 minutes and compare to delay in disappearance of this acid noted in coronary patients.

was still quite high at 60 minutes in the coronary group (Fig. 1).

The heparin-sensitive lipid pool was also tested by infusion of heparin after the infusion of NE. The response in normals was similar to that response after heparin without NE (Table VI). However, in the coronary group there was a significant increase in total FA as well as C 16:0 and C 18:0 when compared to that group's response to heparin alone at 5 minutes. At 10 minutes, these changes within the coronary group were not evident. However, at this time there were significantly higher levels of C 14:0 and C 16:0 in the coronary group than the normals (Table VI, Fig. 2).

An additional observation noted was that although very high levels of both total and individual FFA were reached after NE and heparin, the decrease in FFA was very similar after 30 minutes so that the rate of decline of FFA was much faster after the higher levels (Fig. 3).

Discussion

NE infusion is known to be a potent stimulus for lipid mobilization from adipose tissue.[7] The measure of such a response in man has been studied and the subsequent rise in plasma FFA has been found to be dose dependent.[3] That any difference might exist, however, in the response to NE between healthy normal volunteers and patients with past history of myocardial infarction has not been clear. From our results it would appear that the increases in plasma FFA, both total and individual acids measured after NE, would tend to occur somewhat slower and to a significantly lesser degree in the coronary group when compared to normals. Nestel, comparing coronary and what he regarded as control groups similar in age with the same dosage of NE used in our study, also found total FFA responses to be somewhat greater in the control subjects. On the other hand, Corcoran[8] used smaller doses of NE and

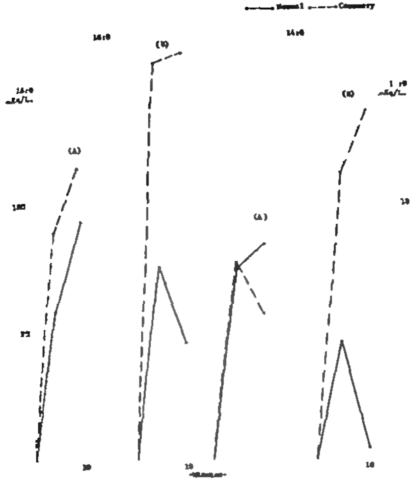

Fig. 2. Mean changes of palmitic (C 16:0) and myristic (C 14:0) acids from the baseline after heparin (A) and after NE-heparin succession (B). Note significant increase in these acids after (B) in the coronary subjects.

Table VI. Additive effect of NE and heparin: mean changes after heparin with and without previous NE

	5 minutes					10 minutes				
	Normal		Coronary			Normal		Coronary		
	H	*H NE*	*H*	*H NE*	*N vs. C*	*H*	*H NE*	*H*	*H NE*	*N vs. C*
C 14:0	7.5	4.7	7.8	11.2	0	8.5	0.5	5.8	13.6	0.05
C 16:0	59	76	90	135 (0.05)	0	94	47	115	159	0.05
C 16:1	9	15	[illegible]	24	[illegible]	14	3	23	17	[illegible]
C 18:0	12	23	9	31 (0.05)	0	17	16	16	31	0
C 18:1	76	133	125	178	0	126	85	170	178	0
C 18:2	36	43	39	45	0	54	32	57	37	0
Total	201	291	287	430 (0.05)	0	318	180	388	387	0

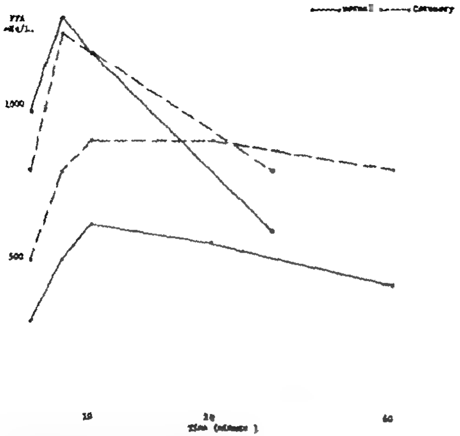

Fig. 3. Comparison of decrease in mean plasma FFA in relation t pre-existing levels of these FFA. Note the more rapid decline in concentration after the higher levels attained by NE-heparin in succession (open circles). Closed circles represent plasma FFA after hepari alone.

compared responses between coronary patients and apparently healthy patients of similar age and found no significant differences in total FFA. Individual acids were not studied.

Our results show that, when the changes in the percentages of the individual FFA to the total FFA are subjected to statistical analysis, there are significant increases in oleic acid and decreases in stearic acid in both normal and coronary subjects, an effect consistent with lipolysis of adipose tissue which contains more oleic and less stearic acid than plasma FFA in the fasting state, as determined by Hirsch and associates.[14] Although we found no significant differences between the coronary group and normal subjects in respect to differences in percentage of individual acids to the total, there was the suggestion that C 16 1 palmitoleic acid increased substantially less in the coronary group. Although Hirsch and his associates[1] declined to interpret how meaningful small changes in adipose tissue composition might be, it is interesting to note on inspection of their tables that percentage of C 16 1 is somewhat less in patients with acute myocardial infarction when compared to normal subjects.

Our results also reveal a significantly greater rise after heparin of C 16 1 in the plasma of the coronary group than in normal subjects. This was also found to be true when percentages of the total were determined. This finding is seemingly paradoxical when compared to the possibility discussed above that there is less C 16 1 in the adipose tissue of these patients. Since TG would tend to reflect more closely the adipose tissue FA in the fasting state, one would have expected less C 16 1. In support of this, we found similar responses in both groups in increased percentage of oleic acid and decreased stearic acid after heparin, just as we did after NE. Thus to explain an increased C 16 1 one would have to postulate either a chronic preferential release of this acid from adipose tissue

in the fasting state of the coronary group or an increased conversion in the liver from more saturated FA (C 14·0 C 16·0) to C 16 1

Carlsten and co-workers[11] studied the arteriohepatic venous differences of FFA and found the A V differences of the saturated and monounsaturated FA to decrease with increasing chain length explaining this finding by the possibility that the shorter chains are used by the liver for synthesis of FA with longer chain length. The increase in C 16 1 in our coronary patients would thus possibly be related to some metabolic difference in the liver of these patients.

Although the decrease in FFA tended to be slower after it had reached its peak after heparin in the coronary group the only significant difference in the two groups was for stearic acid the level of which was still quite high at 60 minutes after injection in the coronary group Carlsten and co-workers[11] found that no significant arteriohepatic venous difference of stearic acid was observed and concluded that it differs in many respects metabolically from other long chain fatty acids The reason that it acted differently in only our coronary patients is obscure however and may be less related to liver metabolism than to peripheral uptake.

It is of interest retrospectively that one of us (L. A. S) has found increased levels of stearic acid after glucose tolerance tests in coronary subjects.[12] At that time we postulated a decrease in the inhibition of release of stearic acid in these patients This explanation appears unlikely in view of the present findings.

It has been noted by Klein and associates[2] that following NE infusion there is a fall in FFA which suggests that such an infusion may inhibit endogenous lipid mobilizing mechanisms. We thus chose also to test the heparin-sensitive lipid pool by infusing heparin after infusion of NE was completed a procedure which would tend to minimize any superimposition of endogenous catecholamines and perhaps reflect a truer effect of heparin Ten minutes after this infusion we found significantly higher levels of C 14·0 and C 16·0 in the coronary group. One cannot compare these effects completely with those found after heparin alone since the NE infusion was expected to change the levels of FA s and indeed to have caused the liver to have metabolically changed many of these acids. Havel and Goldfien [3] injected labeled palmitic acid-1-C[14] intravenously in dogs and found the appearance of radioactivity in TG within minutes and noted that the specific activity of these TG FA exceeded that of FFA after 30 minutes. The significant differences noted above in myristic and palmitic acid would have occurred 30 minutes after NE infusion was begun (10 minutes after heparin) and thus reflect to some degree the changes in FFA and TG imposed by the liver

We find it extremely interesting that with such a significantly greater response in normal subject to NE one would have expected an increased formation of TG in the liver the formation of which would have been noted by an even more marked increase in FFA after heparin (Table I) On the contrary the finding of increased C 14·0 and C 16·0 in the coronary group as well as the significantly greater rise in total FFA than after heparin alone in this group leads one to suspect that perhaps the FA s in normal subjects were slower to be metabolized by the liver were retained by it, or were preferentially released in other moieties, e.g. cholesterol esters or phospholipids.

Nestel in patients with coronary artery disease given labeled palmitate and linoleate found decreasing turnover of linoleate and increased turnover of palmitate with increased TG levels. Thus the increased turnover of palmitate in coronary subjects might be the reason for the significant increase in the appearance of this acid as well as myristic and 30 minutes after the infusion of NE Furthermore Friedberg and Estes[13] have shown that small amounts of myristate can be formed in the liver from acetate derived from the breakdown of carboxyl labeled palmitate

Lastly of some interest is that the higher the level attained the more rapid the decline of FFA in both coronary and normal patients. Armstrong and colleagues also showed that the turnover rate of plasma FFA is related quantitatively to the prevailing plasma FFA concentration. Challoner and Steinberg[4] have found in in vitro perfusion of isolated rat hearts that, at high levels of perfusate FFA there is an increased

utilization of these FA and a concomitant increase in oxygen consumption. They discuss the implications of such a hypermetabolic response to FFA mobilization in which it would seem to be of some importance if one considers the possibility that the increased metabolic rate imposed upon the individual by an acute rise in plasma FFA might be a further imposition on an already ischemic myocardium.

We believe our findings support previous investigations which have found increases in the more saturated FA in the plasma of patients with coronary artery disease and suspect (as does Ahrens) that this is a reflection of lipogenesis from carbohydrate. We believe also that it is very likely that some differences exist in the way these FA are handled by the liver as well as the peripheral tissues in coronary patients and in normal young subjects.

Summary

NE (0.2 μg per kilogram per minute) and heparin (100 mg. intravenously) were used to learn whether their respective lipolytic effects would reveal changes in the plasma FFA that might differ in subjects with a history of myocardial infarction and in young normal subjects. FFA increases in plasma after NE occurred slower and to a significantly lesser degree in the coronary group. Although the pattern change of FFA was similar in both groups and reflected lipolysis of adipose tissue, there was substantially less rise in percentage of palmitoleic acid in the coronary. The heparin-sensitive lipid pool in the coronary group contained significantly more palmitoleic acid than the normal both in terms of absolute amount and as percentage of total FFA. Sixty minutes after heparin there was a significantly greater amount of stearic acid still present in the plasma of the coronary group than in normal group. Heparin was also given 5 minutes after NE infusion was stopped. Ten minutes later there was a significantly greater increase in the two saturated acids myristic and palmitic in the coronary group. The rate of decline of total and individual FFA was much faster after the higher levels of FFA which were reached by combined effect of NE and heparin.

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REFERENCES

1. Soloff, L. A., Cortes, F., and Winters, W. L., Jr.: Importance of myocardial reserve in determining heart rate in levarterenol infusion, Circulation Res. 8:377, 1960.
2. Klein, R. F., Estes, E. H., Jr., and Bogdonoff, M. D.: Effect of norepinephrine on plasma free fatty acid level in man, J. Appl. Physiol. 16:342, 1961.
3. Sunderman, F. W., and Sunderman, F. W., Jr.: Lipids and steroid hormones in clinical medicine, Philadelphia, 1960, J. B. Lippincott Company, p. 45.
4. Soloff, L. A., and Schwartz, H.: Interaction of glucose metabolism and smoking and its effects on phospholipid fatty acids, Am. J. M. Sc. 247:580, 1964.
5. Soloff, L. A., and Schwartz, H.: Erythrocytic phospholipid linoleic acid in ischemic heart disease and health, Lancet 2:1268, 1964.
6. Jover, A.: A technique for the determination of serum glycerides, J. Lip. Res. 4:228, 1963.
7. Havel, R. J., and Goldfien, A.: The role of the sympathetic nervous system in the metabolism of free fatty acids, J. Lip. Res. 1:102, 1959.
8. Nestel, P. J.: Plasma triglyceride concentration and plasma free fatty acid changes in response to norepinephrine in man, J. Clin. Invest. 43:77, 1964.
9. Corcoran, A. C.: Serum free fatty acid and pressor responses to norepinephrine in healthy subjects and in those with ischemic heart disease, Am. Heart J. 67:489, 1964.
10. Hirsch, J., Farquhar, J. W., Ahrens, E. H., Jr., Peterson, M. L., and Stoffel, W.: Studies of adipose tissue in man, Am. J. Clin. Nutrition 8:499, 1960.
11. Carlsten, A., Hallgren, B., Jagenburg, R., and Werko, L.: Arteriohepatic venous differences of free fatty acids and amino acids, Acta med. scandinav. 181:199, 1967.
12. Soloff, L. A., and Schwartz, H.: Relationship between glucose and fatty acid in myocardial infarction, Lancet 1:449, 1966.
13. Havel, R. J., and Goldfien, A.: The role of the liver and of extrahepatic tissues in the transport and metabolism of fatty acids and triglycerides in the dog, J. Lip. Res. 2:389, 1961.
14. Nestel, P. J.: Metabolism of linoleate and palmitate in patients with hypertriglyceridemia and heart disease, Metabolism 14:1, 1965.
15. Friedberg, S. J., and Estes, E. H., Jr.: Tissue distribution and uptake of endogenous lipoprotein triglycerides in the rat, J. Clin. Invest. 43:129, 1964.
16. Armstrong, D. T., Steele, R., Altszuler, N., Dunn, A., Bishop, J. S., and DeBodo, R. C.: Regulation of plasma free fatty acid turnover, Am. J. Physiol. 201:9, 1961.
17. Challoner, D. R., and Steinberg, D.: Effect of free fatty acid on the oxygen consumption of perfused rat heart, Am. J. Physiol. 210:280, 1966.

Disappearance of the Q-deflection following myocardial infarction

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Important changes occur in the QRS complex of the electrocardiogram (ECG) during the course of myocardial infarction. These include the development of abnormal Q-deflections in one or more leads and the appearance of intraventricular block of a specific kind ("peri-infarction block"). Although both of these abnormalities tend to persist indefinitely, at times either one or both may disappear completely. The disappearance of abnormal Q waves results in an ECG which is no longer diagnostic of previous infarction. This report summarizes the information obtained from a review of serial ECG's in which Q-deflections of diagnostic proportions have disappeared during a 10 year period of observation of patients with myocardial infarction. Of particular interest was the number of patients in whom disappearance of abnormal Q-deflections occurred as a naturally evolving phenomenon not related to the development of left bundle branch block or due to subsequent infarction. The study of peri-infarction block is being reported elsewhere.

Methods

Serial ECG's of 775 patients with myocardial infarction seen at the University of Oklahoma and Veterans Administration Hospitals from 1956 through 1966 were reviewed. In each case, significant Q-wave abnormalities (at least 0.04 second in duration) were present initially in one or more leads. Patients with both recent and moderately recent myocardial infarctions were included. Patients with unequivocal evidence of old myocardial infarction were included when the date of infarction could be documented. Those ECG's which displayed only R-ST and T wave abnormalities in the absence of significant Q-wave changes were rejected as being nondiagnostic. At the Veterans Administration Hospital only Leads I and aV were recorded with the standard precordial Leads V to V and V and V (electrode placed to the left of the spine at the level of V). The sensitivity as well as the specificity of this lead system is equivalent to the standard 12 lead ECG. Standard 12 lead ECG's with the addition of V and

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\'s were recorded at the University Hospital Each case had an average of eight ECG's for appraisal Those which showed complete disappearance of pathologic Q-wave abnormalities and reappearance of the R waves were classified accordingly At least three of the authors had to agree that previous myocardial infarction could not be diagnosed or suspected from examination of these ECG's. ECG's displaying small persistent Q-deflections or were otherwise equivocal and might be passed as normal without previous ECG's for comparison were *not* included *in* this group Complete left bundle branch block was defined as prolongation of the QRS complex (0 12 second or more) with absence of Q waves in limb Lead I and in precordial leads to the left of transition Intraventricular block (left) was defined as prolongation of the QRS complex (0 11 second or greater) and delay of the intrinsicoid deflection in the left precordial leads without significant Q-wave abnormality

Hospital records of all 775 patients selected for this study were reviewed for age sex duration of follow up mortality rate and cause of death pre-existing cardiovascular diseases and serum glutamic oxaloacetic transaminase (SGOT) values.

Results

The incidence and time of disappearance of Q-wave abnormal ties are summarized in Table I Of the 775 cases reviewed 52 or 6 7 per cent showed complete disappearance of pathological Q waves. The majority disappeared by the end of two years while the longest recorded time for reversion was six years. Six patients showed regression of pathological Q-deflections within one month of an acute myocardial infarction the shortest time being six days. In one other patient persistent complete left bundle branch block developed on the second day postinfarction Nearly 16 per cent of the group that was followed from one to five months lost evidence of infarction Of 53 patients who were followed from 7 to 10 years none displayed significant alteration of their electrocardiographic evidences of infarction. Fig 1 shows an example of the return of R waves following anteroseptal myocardial infarction

Many of the study group were followed only during the acute phase of their infarctions The known mortality rate of the over all group was 23 per cent. If adjustments are made for the immediate mortality rate the true incidence of the evolution of Q-wave abnormalities would approach 10 per cent. For example the mortality rate in the group followed less than one month was 31 per cent. If these patients had lived from 5 to 15 per cent might have developed nondiagnostic ECG's. Moreover if the subjects who died are excluded the disappearance of abnormal Q waves in the surviving group becomes 7 per cent instead of 4 5 per cent.

An additional 40 patients (5.3 per cent) had borderline electrocardiographic evi

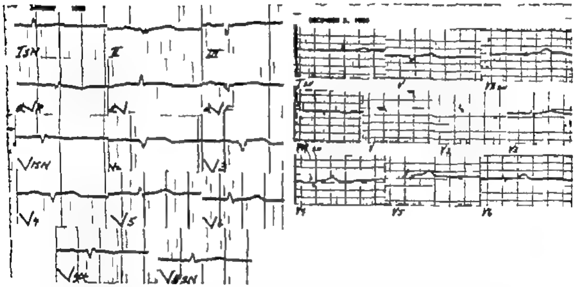
Table I Incidence and time of disappearance of Q waves

Duration of follow-up	Total No.	Disappearance of Q waves		Equivocal Q waves	
		No.	Per cent	No.	Per cent
< 1 month	157	7	4 5	4	2 5
1 to 5 months	82	13	15 9	8	9 8
6 to 11 months	58	2	3 4	6	10 3
1 to 2 years	136	13	9 6	9	6 6
3 to 4 years	1 6	10	5 7	7	4 0
5 to 6 years	113	7	6 2	5	4 4
7 to 10 years	53	0	0	0	0
Total	775	52	6 7	39	3 2

dence of myocardial infarction which could not be diagnosed unequivocally without reference to previous records. These patients were no different with respect to location of infarction duration of follow up age, sex, and other factors studied In effect then about 12 per cent of the original 775 ECG's became nondiagnostic for infarction over the 10-year period of observation

Table II gives the mechanism of disappearance of Q waves as related to the electrocardiographic location of infarctions. One half of the infarctions in the group of 52 were located in the anteroseptal or lateral regions and were slightly more common than those occurring in the inferoseptal or posterior regions (35 per cent) Fifteen per cent involved both the anterior and posterior regions. There was

A



B

Fig. 1 Evolution of changes of acute infarction resulting in loss of diagnostic QRS changes of infarction A th ECG show changes of an acut terœeptal myocardial infarction B the tracing recorded nearly eight years later show normal R progression across the precordium. I terval tracings showed gradual return of the R deflection in Leads V to V Incomplete right bundle branch block is present in both ECG's.

Table II. Mode of disappearance of Q waves by location of infarction

Location	*N*	*Normal evolution*		*Left bundle branch block*		*Intraventricular block*		*Second myocardial infarction*	
		N	*Per cent*	*N*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Anterior	26	20	76	2	8	1	4	3	12
PIB	1	—		—		1			
Posterior	18	9	50	4	22	5	28	0	0
PIB	4	—		2		2			
Anterior and posterior	8	7	88	0	0	0	0	1	12
Total	52	36	69	6	12	6	12	4	8

PIB designates peri-infarction block. Also, numbers for PIB are included in the anterior and posterior categories.

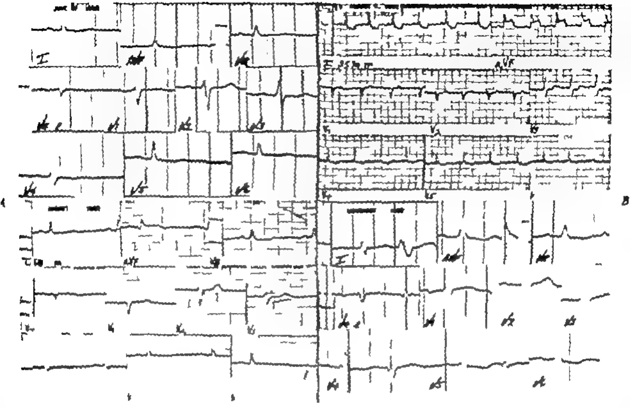


Fig. 2. Development of left ventricular conduction disturbances associated with disappearance of diagnostic Q waves. A, ECG recorded during brief episode of chest pain demonstrates normal QRS interval and T-wave changes. B, the electrocardiographic changes are diagnostic of acute injury and ischemia of the inferoseptal region. In addition, the QRS interval is prolonged (0.12 second), suggesting acute peri-infarction block. C, the tracing taken the following day shows typical changes of an inferoseptal myocardial infarction and peri-infarction block. D, three months later, the QRS remains prolonged but Q waves are absent in normally conducted beats. The intrinsicoid deflection in the left precordial leads is delayed. Note the occurrence of infarct premature ventricular complexes with the bigeminal rhythm.

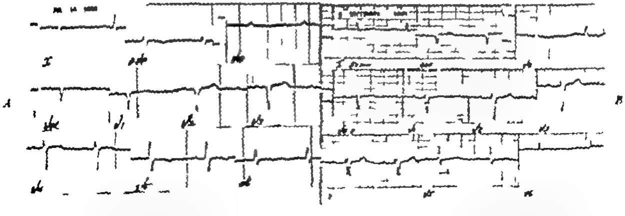


Fig. 3. Regression of QRS changes due to subsequent infarction. A, ECG recorded eight months following anteroseptal myocardial infarction shows Q-S deflections in V and V. B, R-deflection reappears in the anteroseptal region with the occurrence of inferoseptal infarction four years later.

no significant difference for the time of disappearance of Q waves for the different locations of infarction

In six instances, the onset of left bundle branch block obscured the diagnosis of a known previous infarction. An additional six cases manifested left intraventricular block associated with the loss of abnormal Q waves. It is noteworthy that only 9 6 per cent of the group of 52 patients developed peri infarction block. This is contrasted against an over-all incidence of peri-infarction block of 37 per cent in the entire group of 775 patients. Also it is interesting to observe that all five patients initially having peri infarction block retained some form of intraventricular conduction disturbance, either left bundle branch block or intraventricular block. The ECG s shown in Fig 2 demonstrate the loss of abnormal Q waves associated with intraventricular block or incomplete left bundle branch block (QRS 0 10 second)

In four cases or 8 per cent, the disappearance of Q wave abnormalities occurred simultaneously with the onset of a second myocardial infarction. An example of this phenomenon is depicted in Fig 3 In the remaining 36 cases, Q wave disappearance was apparently due to recovery of the initial electrical potentials in the infarcted area.

For the group of patients that showed regression of Q waves, the mean SGOT value during the acute phase of their infarction was 126 units, while the mean value for the over all study group was 201 units. The known mortality rate due to cardiovascular causes in those patients with regression of Q waves was 21 per cent. This mortality rate is not significantly different from the 23 per cent mortality rate recorded for the over-all group

Discussion

Nearly 5 per cent of the 775 patients observed in this study had ECG s indistinguishable from normal in the 10-year period following infarction. This differs somewhat from other studies where the incidence has been reported variously from 1 8 to 76 per cent However our figure compares favorably with that reported by Kaplan and Berkson[3] who found that 6 per cent of 251 middle-aged men surviving the first eight weeks after infarction had normal ECG s within 3½ years. In their study 34 per cent of those with nontransmural infarctions had normal ECG s at the end of the same period Also they pointed out the long term mortality rate was not significantly different in patients with transmural and nontransmural infarctions as well as in those with disappearance of Q waves. In our study the majority of ECG s with abnormal Q waves that regressed did so by the end of two years with a small percentage reverting to normal up to six years following acute myocardial infarction. Thus, the ECG may be normal in about one out of 20 patients from a few weeks to a few years following acute myocardial infarction It may be equivocal in an additional 5 per cent giving a total of one out of 10 tracings which are nondiagnostic.

The lower SGOT values of patients showing regression of Q waves suggests that their infarctions were less extensive. The same findings were reported by Andersen and Skjaeggestad The rarity of peri-infarction block in the group which lost Q waves supports this concept because the presence of peri-infarction block seems to imply a more extensive infarction. Also none of the patients who had peri-infarction block lost Q waves except when other intraventricular conduction disturbances occurred

The precise mechanism of regression of abnormal Q waves is not known. Presumably when the infarcted area is small shrinkage occurs gradually during healing and viable muscle covers the scarred area. Adequate collateral circulation during the early healing phase is no doubt important. However there does not appear to be a relationship between regression of Q waves and the patient s age even though it could be postulated that collateral circulation might be better in the younger patient with less extensive coronary artery disease.

It is natural for clinicians to assume that reversion of the ECG to normal following myocardial infarction implies a more favorable prognosis However the mortality rate experience of this study as well as that previously cited clearly indicates that those patients with normal or nondiagnostic ECG s following myo-

cardial infarction do not have a more favorable prognosis.

It has long been recognized that the onset of left bundle branch block will mask electrocardiographic evidence of a previous myocardial infarction. This phenomenon occurred in six cases (about 1 per cent) and accounted for about one-eighth of those without abnormal Q waves following infarction. Shanoff and Little[5] noted 4 per cent of their subjects developed complete left bundle branch block. The occurrence of left bundle branch block was more common in the group of patients with posterior or inferoseptal infarctions. This phenomenon may occur because the blood supply of the proximal portion of the left bundle branch is usually derived from the septal branch of the right coronary artery. Therefore, infarctions of the posterior region might be expected to involve the bundle of His or its major branches similar to the observed frequency of abnormal atrioventricular (AV) nodal conduction.

The acute mortality rate of patients who develop intraventricular conduction disturbances during myocardial infarction is increased significantly. In addition, we have observed an increased mortality rate associated with peri-infarction block during the first year following myocardial infarction. However, the mortality rate of the 12 patients in this study with abnormal intraventricular conduction was 75 per cent, or essentially the same as the over all group.

The ECG's of four patients in the present study displayed loss of significant Q waves with or subsequent to the onset of a second myocardial infarction. Such an event is likely due to loss of opposing electromotive forces which were responsible for the initial dead zone effect.[12]

Summary

Serial ECG's of 775 patients followed from one month to 10 years after myocardial infarction were reviewed. A significant number, 6.7 per cent, showed disappearance of abnormal Q waves, and an additional 5.2 per cent showed only equivocal Q wave changes related to previous infarction. In those cases where the Q wave abnormality disappeared, the majority (69 per cent) regressed coincidentally with healing of the infarcted area. In only about one-eighth, left bundle branch block supervened to mask the electrocardiographic evidence of previous infarctions. Additional factors leading to regression of the Q-deflection were the development of intraventricular blocks other than bundle branch block (12 per cent) and the subsequent occurrence of myocardial infarction (8 per cent) obscuring the evidences of previous infarction. The majority of the ECG's which showed disappearance of significant Q-deflections did so within two years following infarction; none changed after six years. The disappearance of abnormal Q-deflections in the ECG was not associated with a better prognosis in these patients.

REFERENCES

1. Shadaksharappa, K. S., Kalbfleisch, J. M., Conrad, L. L., and Sarkar, N. K.: Recognition and significance of intraventricular block due to myocardial infarction (peri-infarction block), *Circulation* 37:20, 1968.
2. Schaffer, A. I., Blumfield, S., Buxman, R., and Scherf, D.: A new look at electrocardiographic leads, AM. HEART J. 52:704, 1956.
3. Kaplan, B. M., and Berkson, D. M.: Serial electrocardiograms after myocardial infarction, Ann. Int. Med. 60:430, 1964.
4. Andersson, N., and Skjaeggestad, O.: The electrocardiogram in patients with previous myocardial infarction, Acta med. scandinav. 176:123, 1964.
5. Shanoff, H. M., and Little, J. A.: Studies of male survivors of myocardial infarction. VI. The electrocardiogram, Canad. M. A. J. 93:1049, 1965.
6. Woods, J. D., Laurie, W., and Smith, W. G.: The reliability of the electrocardiogram in myocardial infarction, Lancet 2:265, 1963.
7. Pappas, M. F.: Disappearance of pathological Q waves after cardiac infarction, Brit. Heart J. 20:123, 1958.
8. Gittler, R., Schack, J. A., and Vesell, H.: The electrocardiogram one year after acute myocardial infarction, AM. HEART J. 51:246, 1956.
9. Bohm, C.: Über elektrokardiographische Spätveränderungen nach Herzinfarkten, Med. Welt (Berl.) 18:798, 1962.
10. Gross, L.: The blood supply to the heart, New York, 1921, Paul B. Hoeber, Inc., p. 42.
11. Hughes, W. L., Kalbfleisch, J. M., Brandt, E. N., Jr., and Costiloe, J.: Myocardial infarction prognosis by discriminant analysis, Arch. Int. Med. 111:338, 1963.
12. Bayley, R. H.: Electrocardiographic analysis, vol. 1, Biophysical principles of electrocardiography, New York, 1958, Paul B. Hoeber, Inc., p. 98.

Experimental and laboratory reports

Atrial synchronized pacemaker arrhythmias: Revisited

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Synchronized pacemakers have been used successfully in the treatment of Stokes-Adams attacks.[1-7] Their major advantage lies in the correction of the A-V block by artificially restoring a physiological atrioventricular conduction. Although this feature has resulted in an improvement of the efficiency of the heart, other arrhythmias, some simple, some more complex, have been produced. Various disorders of rhythm appearing after the implantation of synchronized pacemaker were presented in 1964.[8] Several authors have had similar experiences.[7, 9-11] It is evident that a thorough knowledge of the unusual electrocardiograms (ECG's) is indispensable to an understanding of the proper behavior of these units. Such an assumption is well illustrated in the following report, which also emphasizes certain sophisticated aspects of their performance. In addition heretofore undescribed iatrogenic dysrhythmias will be presented. They were artificially created to further evaluate the responses of the artifical pacemaker.

True and false atriosynchronized pacemaker escapes. Conventional electrocardiographic theory holds that an escape should appear after a specific interval without ventricular contraction has been exceeded.[12] The pause between the escape beat and the previous R wave has to be longer than the basic R-R intervals.[12] This is a prerequisite for, if this were not so, the beat under consideration would not be an escape but an extrasystole. It should be pointed out that atriosynchronized escapes do not depend on their distance from the preceding R wave, for they occur when a pre-set interval without an effective atrial contraction is exceeded. This refers to P waves appearing after the end of pacemaker refractoriness for those falling before completion of the latter will be invariably blocked.

The differences between "true" and "false" atriosynchronized pacemaker escapes are schematized in Fig. 1. The top strip shows normal atriopacemaker synchronization. [illegible] ly [illegible] extrasystole occurs [illegible] end. This ectopic atrial contraction [illegible] unable [illegible] the

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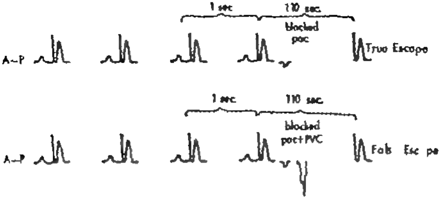

Fig. 1. Differences between true and false atriosynchronized escapes. *pac*, Premature atrial contraction. *pac + PVC* indicates the association of premature atrial contraction and a ventricular extrasystole.

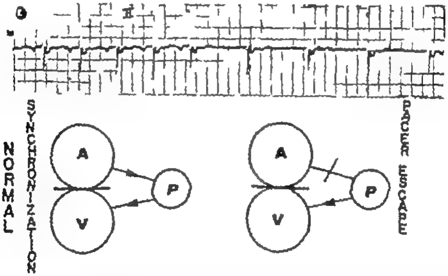

Fig. 2. Unusual form of synchronized pacemaker escapes occurring after carotid sinus pressure. The center stimulating the pacemaker is located in the A-V node (in this and following diagrams, *A* represents the atria, *P* the synchronized pacemaker, and *V* the ventricles. The solid horizontal line between A and V indicates total blockage of impulse from atria to ventricles through the anatomical A-V junction and vice versa. The arrows from *A* to *P* and from *P* to *V* shown in the left-sided schematics indicate that the atrial deflection is picked up by the pacemaker which in turn depolarizes the ventricles. The right-sided schematic shows an oblique broken line between *A* and *P* indicating that the corresponding pacemaker discharges are not triggered by the atrial impulse. All figures are fully described in the text.

pacemaker since it falls in the refractory period of the latter. In consequence the pacemaker will escape after a pre-set interval during which it has not received an effective atrial stimulus. The lower strip illustrates a similar sequence of events. However, now the blocked premature atrial contraction is followed by a ventricular extrasystole. A pacemaker "escape" occurs at the preselected time in spite of the ectopic ventricular contraction because the instrument fires when it does not receive an effective atrial stimulus, irrespective as to whether or not this discharge is preceded by a QRS complex. It is important to emphasize that the extra beat is not sensed. The pacemaker induced QRS complex is not a true escape since it is preceded by *a pause which is not longer (in fact shorter)* than the basic R-R interval.

Fig. 2 shows true pacemaker escapes during a period of sinoatrial slowing in

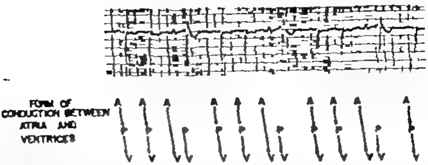

Fig. 3. False pacemaker escapes falling close to the peak of an antecedent T wave. In this diagram, *A* indicates the atria, *P* the pacemaker, and *V* the ventricles. Normal pacemaker synchronization is represented by the *A-P-V* sequence. *A-V* indicates transmission directly from the auricles to the ventricles through the anatomical junction. *P-V* represents pacemaker "escapes" not triggered by an atrial contraction.

duced by carotid sinus massage. The unusual feature of this case is that the pacemaker is triggered by impulses originating in the A-V node instead of in the sinus node. The P waves are inverted not only in Lead II but on III and AVF as well (not shown). They discharge the pacemaker with an A-P conduction time of 0.20 sec. Note that carotid sinus stimulation inhibits impulse formation in the A-V node so that the pacemaker escapes passively at a rate of 54 per minute. The interval preceding the escape is longer than the basic R-R distance.

Fig. 3 starts with two normally synchronized beats. This is shown in the diagram presented below the strip. The atrial contractions, having a rate of 97 per minute, stimulate the pacemaker after an interval of 0.20 sec. The large stimulus artefacts are diphasic (positive-negative). They are followed by hardly visible QRS complexes. The corresponding (negative) T waves are well delineated. The third P wave fails to stimulate the pacemaker. Since the natural A-V pathways were patent at this moment, the atrial contraction was propagated to the ventricles via the anatomical A-V junction. This P-R interval measured 0.22 sec., that is, 0.02 sec. longer than the atrio-pacemaker conduction time. The next ventricular contraction was triggered by the pacemaker which was activated when it did not receive an effective atrial contraction. It "escapes" at the preselected interval, not detecting the previous (sino-atrial) QRS complex. The stimulus artefact falls close to the peak of the T wave of the conducted beat and induces an aberrant ventricular complex. This is a classical feature of stimulation during the relative refractory period. The following atrial deflection falls inside the aberrant ventricular beat. It is blocked, for it occurs during the refractory period of both natural and artificial atrioventricular connections. The next two atrial deflections again are able to stimulate the pacemaker, reinitiating a series of events similar to the ones just described. In this case the idiopacemaker beat is not a true "escape" because its distance to the previous R wave is not longer than the basic R-R intervals. False escapes represent one mechanism by which an atriosynchronized stimulus might fall in the vulnerable period.

Figs. 1 to 3 indicate that, although the atriosynchronized pacemaker is indeed capable of operating on an escape basis, this feature per se is not enough to include it in the same category as the demand[13] or stand-by units. The latter also work on an escape basis, but these beats are conditioned by the absence of ventricular (not atrial) contractions. Hence, under normal conditions the demand pacemaker should always be preceded by pauses which are longer than the basic R-R intervals.

Ectopic ventricular contractions resulting in pacemaker stimulation during vulnerable phase. Atrial synchronized pacemaker spikes can fall in the T wave of interpolated ventricular extrasystoles by another mechanism. The iatrogenic production of such an arrhythmia is seen on Fig. 3. The ECG

was obtained from a patient with complete A-V block one day after implantation of the synchronous unit, at a time in which a transvenous catheter was still inside the right ventricular cavity. The implanted pacemaker is depolarizing the ventricles at a rate of 80 per minute (R-R intervals of 0.75 sec.). Large diphasic (negative-positive) stimulus artefacts follow the atrial stimulus at fixed intervals. The corresponding QRS complexes display a right bundle branch block (RBBB) pattern. In addition, there is a second transvenous pacemaker discharging at a rate of 53 per minute. All spikes produced by this pacemaker are small but positive. They are numbered at the top of the strip. The corresponding ventricular complexes show a left bundle branch block (LBBB) morphology, indicating a right-to-left spread of activation. Other tracings of this patient with a double artifical parasystole have been published elsewhere.[18]

The first stimulus artefact of the transvenous pacemaker falls in the refractory period of the ventricles, and therefore is unable to produce a propagated response. It is interesting to note that the second stimulus appears immediately before the implantable stimulus. A fusion beat results when the ventricles are depolarized simultaneously from both left and right pacemakers. The third spike from the transvenous pacemaker occurring after the end of ventricular refractoriness is able to stimulate the ventricles. A sinoatrial impulse (A) follows this ventricular deflection and activates the pacemaker after the usual atriopacemaker time. The resulting spike follows the peak of the T wave. Therefore the LBBB beat is interpolated. Similar events follow the ventricular deflections produced by the fifth right ventricular stimulus artefact. At this moment, however, the stimulus from the left ventricular pacemaker falls slightly after the peak of the T wave during the relative refractory period. Thus, the corresponding QRS complex shows a bizarre appearance instead of the usual RBBB pattern. This distortion is characteristic of stimuli falling before full recovery of excitability. The timing of the ventricular complex produced by the seventh right ventricular stimulation is such that the following atrial stimulus falls before the end of depolarization. Since the atriopacemaker interval remains unaltered, the corresponding spike is pulled toward the absolute refractory period so that it fails to stimulate the ventricle.

Note that the distance between the left ventricular stimulus artefacts is not shortened after the iatrogenic extrasystoles, which indicates that the former are not triggered by the latter. The arrhythmias presented in Figs. 3 and 4 indicate that, under certain conditions, the synchronized pacemaker does not prevent its impulses from falling on the peak of the T wave. Repetitive firing induced by electrical stimuli falling in the vulnerable period, although rare, has been reported by some authors.[12, 13, 26]

Pacemaker captures (by the ventricles). Atriopacemaker dissociation can appear after variable periods of normal synchronization. In these cases, properly timed P waves are able to "capture" the pacemaker assuming complete blockage of impulses through the normal A-V junction. This will depend on the relationship between the sinoatrial and iatrogenic pacemaker rates, the atriosynchronized conduction time, and the length of pacemaker refractoriness. On other occasions, the spike becomes synchronized to the R wave. The ventricles and not the atria now "capture" the pacemaker. Examples of this arrhythmia have been reported after attempted atriopacemaker synchronization.[7-9] Excluded from this group are the patients in whom the stimulus artefacts were synchronized to the R wave on *purpose*. This type of pacing has been considered a form of pacemaking on demand.[27] However, ventriculosynchronized units are not demand in principle since the pacemaker stimulus artefact is, although ineffectively stimulating the ventricular muscle, always present.

According to Nathan and associates, *fortuitous ventriculopacemaker synchronization* indicates that the electrical forces of ventricular activation have enough voltage to stimulate the auricular lead as if they were P waves. In a case reported by Faivre and associates[8] (their Fig. 17) the spikes occurred exclusively after the R wave, even when a P wave stimulated the ventricles with a normal P-R interval through the anatomical A-V junction. The

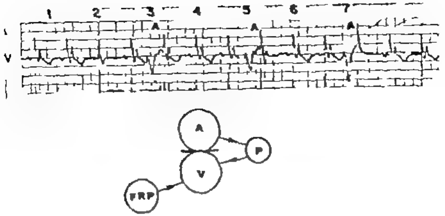

Fig. 4. Double artificial ventricular parasystole showing atriosynchronized pacemaker stimulus artefacts falling in the relative and absolute refractory periods of ectopic ventricular contractions. The synchronized spikes are triggered by a sinoatrial contraction falling within the anomalous QRS complexes. The diagram shows complete blockage of impulses from the atria to the ventricles through the anatomical A-V junction, normal A-P-V synchronization, and the activity of a second, continuous, pacemaker (*FRP*) stimulating the contralateral ventricle.

sinus P wave fell outside the refractory period of the previous stimulus artefact. It seems that the magnitude of the P wave was insufficient to discharge the pacemaker.

Najmi and co-workers[11] described a new form of atrial pacemaker block (see below). Their B_3 in Fig. 3 is very similar to the case of Favre and associates, although interpreted differently by the authors. It probably represented an unusual form of ventriculopacemaker synchronization. Some of the P waves appeared 0.38 sec. after the preceding spike and probably could not activate the pacemaker because of its refractoriness. This P wave was transmitted to the ventricles through the normal A-V junction. The resulting R wave was thereafter responsible for triggering the stimulus artefacts. A prolonged atriopacemaker conduction time (longer than the P-R interval) could be excluded because R-to-spike intervals remained unchanged in the presence of variations of the P-R interval.

The mechanism of production of a similar arrhythmia is presented in Fig. 5. It supports our interpretation of Fig. 3 (B_3) in the article by Najmi and co-workers.[11] The top strip shows normal atrioventricular synchronization. A premature atrial contraction (*A ex*) fails to stimulate the pacemaker. It was also blocked toward the ventricles through the anatomical A-V pathway. As a result of this beat, the pacemaker escapes 0.96 sec. after the last stimulus artefact. The bottom strip also shows a blocked atrial extrasystole which fails to discharge the pacemaker. It is possible that the extrasystole could have reached the ventricles through the anatomical A-V junction with a prolonged atrioventricular conduction time (0.46 sec.). In favor of this assumption was the long P-R interval (0.36 sec.) recorded in other moments. The QRS complex could also have represented an A-V nodal extrasystole. However the exact nature of this beat is irrelevant for the description of the events which took place immediately after. This ventricular complex was followed by a stimulus artefact having an R-to-stimulus distance similar to that existing between the atrial contraction and the stimulus artefact during normal atrioventricular synchronization. The very long distance between the pacemaker stimulus and the preceding P wave makes the possibility of first-degree atrial pacemaker block as conceived by Najmi and co-workers[11] very improbable. Moreover it can be seen that the R-to-stimulus interval remains the same in the presence of a very long, absent, or shorter P-R interval. The stimulus artefacts are unable to stimulate the ventricle because they fall in the refractory periods of the natural

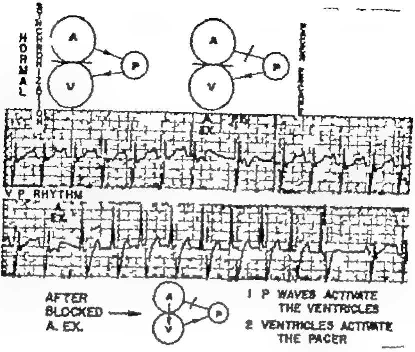

Fig 5 Intermittent pacemaker captures by the ventricles following atrial extrasystoles.

beats. They are followed by atrial deflections which appear during the refractory period of the pacemaker and which are unable to trigger the latter. These atrial contractions stimulate the ventricles via A V node with a prolonged atrioventricular conduction time (0.36 sec.) Note that the spikes follow the ventricles at a rate of 100 per minute, thus excluding the possibility of "passive" pacemaker escapes.

Another atrial extrasystole occurs towards the end of the tracing as indicated by the vertical arrow. It distorts the base line between the QRS and the stimulus artefact. Moreover it inhibits impulse formation in the sinus node so that the next sinoatrial discharge does not occur at the expected time. The following T wave is not distorted by the superimposed atrial deflection. It is interesting that this was not the only detectable effect of the ectopic atrial contraction since in addition it was unable to depolarize the ventricles through either pathway. This extrasystole which ended the bizarre arrhythmia was followed by a pacemaker escape (the A I interval was too short for the atria to trigger the pacer). Finally the strip ends with a normally synchronized beat which reinitiates normal pacemaker function.

Mechanisms by which a stimulus artefact can follow a QRS complex during normal atriosynchronization. There are five different mechanisms by which a stimulus artefact can follow a QRS complex. (1) Other authors have reported that conduction from atria to ventricles can occur simultaneously through both natural and artificial A V communication. If the normal P R interval is shorter than the atrio-pacemaker conduction time the spike will fall at variable distances after the R wave. The other mechanisms are (2) false pacemaker escapes (Fig 2) (3) superimposition of a sinus P with an ectopic QRS complex with preservation of the normal A P synchronization (Fig 3) and (4) V I synchronization (Fig 4) and (5) triggering of the pacemaker by a retrograde P wave (Fig 6).

There is normal A P synchronization in the top strip (Fig 6). The atria trigger the pacemaker after an interval of 0.20 sec. The pacemaker in turn depolarizes the ventricles. There are three ventricular extrasystoles followed by stimulus artefact. In the bottom strip. The first extrasystole stimulates the pacemaker after a V I interval of 0.20 sec. exactly the same as the one recorded during normal atriosynchro-

Fig. 6. Three different mechanisms by which the stimulus artefacts can follow the extrasystolic R waves ( ) V-P synchronization (*Ex. 1*) (b) A-P synchronization by sinoatrial contraction preceding or merging with the ectopic ventricular contraction (*Ex. 2*) ( ) A-P synchronization by the retrograde atrial activation produced by ectopic ventricular contraction (*Ex. 3*). The numbers below the extrasystoles indicate their order of appearance the strip. *A* represents atrial contractions of sinoatrial origin except for A— which is produced by the retrograde conduction of one of the extrasystoles.

nization. This produces a shortening of the interstimulus intervals. The sinoatrial beat falling within the QRS complex could not have triggered the pacemaker because it falls only 0.12 sec. before the parasystolic discharge. The second extrasystole has a different morphology and occurs late in diastole. In fact, it is preceded by an atrial contraction which is responsible (after a delay of 0.20 sec.) for the stimulus artefact falling in the descending portion of the R wave. In contrast to what happened after the first ectopic ventricular contraction, in this instance the ventricles could not activate the pacemaker because the V-P interval measured 0.14 sec., obviously too short for this purpose.

A third extrasystole immediately follows the previous one. Now the stimulus artefact falls after the end of the absolute refractory period of the ventricles (close to the peak of the T wave) and is able to depolarize the latter. The problem at this moment consists in determining what triggered the stimulus artefact. Obviously the long V-P interval of 0.30 sec. excludes a pacemaker capture by the ventricles. However, plotting the atrial cycle revealed that the moment in which the next atrial contraction was expected to fall (indicated by an arrow) would have resulted in a short P-R interval of 0.12 sec., also excluding normal atriopacemaker synchronization. Since the stimulus artefact was not induced by the ventricles nor by the sinoatrial beat, the conclusion seems to be that this extrasystole had retrograde conduction to the atria (A—) and the latter was directly responsible for activating the pacemaker. An A-P conduction time of 0.20 sec. was attained considering that the atrial contraction appeared at the moment indicated by (A—).

Pacemaker captures (by another artificial pacemaker). An unusual form of pacemaker capture (iatrogenic in origin) is presented in the top strip of Fig. 7. In this case it is neither the atria nor the ventricles which capture the synchronized pacemaker, but the stimulus artefacts produced by a second unit. The first four beats show normal atriopacemaker synchronization in patient with established complete A-V block (the P waves appear inverted and the QRS complex upright in Lead I because the arm cables were inadvertently switched). Note that the corresponding stimulus artefacts are large and diphasic (negative-positive). In this patient the stimulating electrodes from a second pacemaker were placed on the precordial area. The sensitivity was adjusted for internal pacing in such a way as to produce a large spike. There was no discomfort to the patient since the current employed did not exceed 5 volts. On attaining sufficient height, this positive stimulus artefact "captured" the synchronized pacemaker. This interesting phe

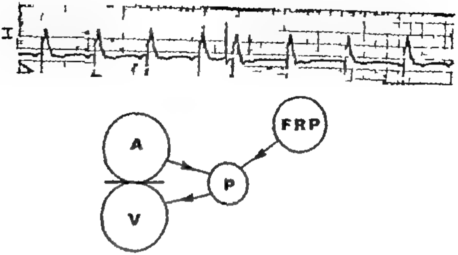

Fig. 7. Synchronized pacemaker captures by the stimulus artefact from second (artificial) pacemaker. The atrial deflections appear inverted because Lead I was obtained with the arm cables switched.

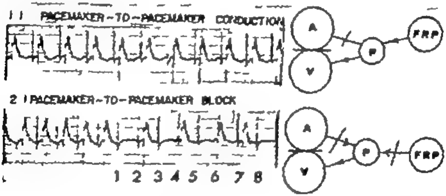

Fig. 8. Unusual type of iatrogenic electrical arrhythmia: pacemaker-to-pacemaker block. The broken lines indicate intermittent A-P and F-P block.

nomenon is seen in the middle of the strip. The pacemaker-to-pacemaker intervals were in the same range as that of the atriopacemaker conduction time. The following P wave fell 0.1 sec. after the preceding synchronized spike, that is, before the end of pacemaker refractoriness. It appears at the end of the QRS complex and is blocked in the artificial atrioventricular connection. In consequence, the synchronized pacemaker escapes at its pre-set interval (0.94 sec.). A succession of escapes leads to a short period of atriopacemaker dissociation. Continuous, instead of intermittent, pacemaker capture produces another interesting arrhythmia if the rate of the fixed rate pacemaker is progressively increased.

Pacemaker to pacemaker block. The most frequent type of iatrogenic heart block occurs in patients with atriosynchronized pacemakers whenever a P wave falls before the end of pacemaker refractoriness. The term second-degree atriopacemaker block has been employed for this conduction disturbance taking place between atria and pacemaker. 2:1 A-P block is the most frequent type, although the 3:1 form can be seen in some patients with atrial flutter. Najmi and co-workers[11] have described a first degree A-P block ascribed to trauma or edema in the regions of the atrial electrode. Less known is the fact that "block" can also occur between two pacemakers related as presented in Fig. 7.

The rate of the continuous pacemaker was increased to 100 per minute in the top strip of Fig. 8. There is 1:1 pacemaker

to-pacemaker conduction On the other hand A P conduction is absent, probably because the atrial impulses on reaching the synchronized pacemaker find that the latter is maintained in a state of constant refractoriness by the continuous unit. In the lower strip the rate of the latter was further increased to 130 per minute, still with 1 1 response. Toward the middle the synchronized pacemaker fails to follow a very driving spike so that 2 1 P P block ensues at a rate of 65 per minute (R R cycle of 0 92 sec.) The numbers indicate the occurrence of stimulus artefacts after the onset of 2 1 P P block The synchronized beat followed by stimulus artefact No. 4 was not triggered by the latter since the interspike distance is too short for this purpose. It occurs in response to the previous atrial impulse and represents a true pacemaker capture (by the atria) since the corresponding QRS complex appears 0 82 sec. after the preceding E wave. This distance is shorter than the pre-set escape interval (0 84 < 0 94) Thereafter stimulus artefacts 5 and 6 fail to activate the pacemaker because they reach the latter during the refractory period created by the normal atrial synchronization. Such a series of events leads to a situation which is exactly the reverse of what was seen on the top strip In the latter the atria could not capture the synchronized pacemaker But now the continuous unit is the one which is unable to activate the synchronized pacemaker

The events shown in this figure indicate that this patient had three different types of block. There is complete A V block between atria and ventricles through the anatomical A-V junction. Impulses from the atria can also be said to be blocked towards the synchronized pacemaker since they fail to stimulate the latter during periods of 1 1 pacemaker to-pacemaker conduction (top strip) Finally there are various types of second degree block between the two artificial units (end of bottom strip)

Discussion

The synchronized pacemaker has been a valuable adjunct in the treatment of various types of A V block. This unit has specific indications as well as definite contraindications. The arrhythmias presented in this communication should not detract from its use. All instruments commonly used in cardiology as well as all forms of therapy employed in clinical medicine, can produce unexpected responses. A description of the unusual reactions to artificial pacemakers should make an accepted form of therapy safer The primary function of the different types of electronic instruments is to provide an effective cardiac contraction whenever the electrical function of the heart fails for one reason or another In addition the secondary gains obtained through the analysis of their normal behavior as well as of their malfunction has increased our knowledge of cardiac and pacemaker electrophysiology The information thus gathered can thereafter be re applied to the proper management of the patient.

Summary

The synchronized pacemaker has proved to be effective in the treatment of symptomatic A V block. However several complex arrhythmias have appeared after its implantation during its normal behavior as well as during its malfunction In some cases, the ectopic rhythms were iatrogenically created with the purpose of studying the response of the pacemaker Four possible mechanisms by which synchronized stimulus artefact could appear during an antecedent T wave were presented Differences between true and false escapes were stressed One tracing showed a rare form of pacemaker capture by a high A V nodal rhythm In another patient, the synchronized pacer was captured by a continuous unit. An increase in rate of the latter led to a previously undescribed arrhythmia, hereby labelled pacemaker to-pacemaker block. In this case there were two different centers competing to capture the synchronized pacemaker The analysis of these arrhythmias has increased our knowledge of clinical and pacemaker electrophysiology

REFERENCES

1 Nathan, D A., Samet, P Center S., and Wu, D A. Long-term correction of complete heart block. Clinical and physiologic studies of a new type of implantable synchronous pacer Progr Cardiovas. Dis. 6:538, 1964.

Nathan, D. A., Center, S., Wu, C. Y., and Keller, W.: An implantable synchronous pacemaker for the long term correction of complete heart block. Circulation 27:682, 1963.
3. Nathan, D. A., Center, S., Wu, C. Y., and Keller, W.: An implantable synchronous pacemaker for the long term correction of complete heart block. Am. J. Cardiol. 11:362, 1963.
4. Center, W., Nathan, D. A., Wu, C. Y., Samet, P., and Keller, W.: The implantable synchronous pacer in the treatment of complete heart block. J. Thorac. & Cardiovas. Surg. 46:744, 1963.
5. Center, S., Nathan, D. A., Wu, C. Y., and Duque, D. T.: Two years clinical experience with the synchronous pacer. J. Thorac. & Cardiovas. Surg. 48:513, 1964.
6. Nathan, D., Center, S., Pina, R. E., Medow, A., and Keller, W.: The synchronous pacer in the therapy of Adams-Stokes disease. Electrocardiographic patterns of response to ectopic cardiac activity. In Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias. New York, 1966, Grune & Stratton, Inc.
7. Chaitot, P., Favre, G., Frech, R., and Cherrier, F.: Utilisation d'un nouveau stimulateur implantable: le pacemaker synchrone de Nathan. Ann. med. Nancy 3:295, 1964.
8. Castellanos, A., J., and Lemberg, L.: Arrhythmias appearing after the implantation of synchronized pacemakers. Brit. Heart J. 26:747, 1964.
9. Faivre, G., Gilgenkrantz, J. M., Frech, R., Cherrier, F., Renaud, J., and Petitier, H.: Les incidences électrocardiographiques de la stimulation électrique par pacemaker synchrone. Arch. mal. Coeur 58:134, 1965.
10. Heidel, H. J., Schwarger, R., and Lemmes, W.: Observation of postoperative disturbance after implantation of A-P controlled pacemaker (Atricor). Zentralbl. Chir. 91:793, 1966.
11. Nimal, M., Segal, B. L., Likoff, W., and Dreifus, L. S.: Atrial-pacemaker block: A new electrocardiographic syndrome associated with implanted synchronous pacemakers. Dis. Chest 48:1, 1965.
12. Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias. Philadelphia, 1956, Lea & Febiger, Publishers.
13. Lemberg, L., Castellanos, A., J., and Berkovits, B. V.: Pacemaking on demand in A-V block. J. A. M. A. 191:1, 1965.
14. Parsonnett, V., Zucker, I. R., Gilbert, L., and Myers, G. H.: Clinical use of an implantable demand pacemaker. J. A. M. A. 196:104, 1966.
15. Castellanos, A., J., Lemberg, L., and Gosselin, A.: Double artificial ventricular parasystole. Cardiologia 4:273, 1965.
16. Dittmar, H. A., Friese, G., and Holder, E.: Erfahrungen über die langfristige lektrische Reizung des menschlichen Herzens. Ztschr. Kreislaufforsch. 51:66, 196.
17. Elmqvist, R., Landegren, J., Pettersson, S. O., Senning, A., and William-Olsson, G.: Artificial pacemaker for treatment of Stokes-Adams syndrome and slow rate. Am. Heart J. 65:731, 1963.
18. Bonnabeau, R. C., J., Bilgutay, A. M., Stern, L. P., Wingrove, R., and Lillehei, C. W.: Observations on sudden death during pacemaker stimulation in complete atrioventricular block, leading to development of P wave pacemaker without atrial lead. Tr. Am. Soc. Artif. Int. Organs 9:158, 1963.
19. Tavel, M. F., and Fisch, C.: Repetitive ventricular arrhythmia resulting from artificial internal pacemaker. Circulation 30:493, 1964.
20. Robinson, D. A., Fabetti, H. L., Wheeler, D. H., Miller, D. B., and Amadon, E. L.: Ventricular fibrillation associated with two functioning implantable cardiac pacemakers. Am. J. Cardiol. 15:397, 1965.
21. Dressler, W., Jonas, S., and Rubin, R.: Observations in patients with implanted cardiac pacemakers. IV. Repetitive responses to electrical stimuli. Am. J. Cardiol. 15:391, 1965.
22. Katz, L. N.: Artificially induced paired and coupled beats. Bull. New York Acad. Med. 41:428, 1965.
23. Langendorf, R., and Pick, A.: Observations on the clinical use of paired electrical stimulation of the heart. Bull. New York Acad. Med. 41:535, 1965.
24. Castellanos, A., J., Lemberg, L., Jude, J. R., and Berkovits, B. V.: Repetitive firing occurring during synchronized electrical stimulation of the heart. J. Thorac. & Cardiovas. Surg. 51:334, 1966.
25. Dalle, X.: The current status of pacemaking. Proceeding of Symposium presented by the American College of Cardiology and the Presbyterian University of Pennsylvania Medical Center. New York, 1966, The Charles Press.
26. Welti, J. J., Fontaine, G., and Facquett, J.: Période vulnérable: risques possibles de rhythmes interférentiels et des stimulations pairées ou couplées chez l'homme. Arch. mal. Coeur 60:50, 1967.
27. Neville, J., Miller, K., Keller, W., and Abildskov, J. A.: An implantable demand pacemaker. Clin. Res. 14:256, 1966.

Total cardiac output response during four minutes of exercise

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Donald and his colleagues and others have repeatedly demonstrated the value of the measurement of cardiac output during muscular exercise as an index of cardiac efficiency. Those studies show that the cardiac output of normal subjects can be predicted with a high degree of accuracy provided the energy expenditure of the body is known. In contrast, the cardiac output of patients with most forms of advanced heart disease is significantly lower than that predicted from the energy expenditure of the body or the rate of work. Striking exceptions to this generalization are those patients with hyperkinetic disorders such as thyrotoxicosis, vasoregulatory asthenia, Padget's disease, and the idiopathic hyperkinetic syndrome. The cardiac output of these patients in response to muscular exercise usually is greater than the predicted value for a normal subject. Studies such as these have been of great value in quantitatively defining some of the hemodynamic abnormalities of patients with heart disease. It is clear, however, that the quantitation of cardiac output during exercise under the conditions of the test gives an incomplete picture of the cardiac output response to muscular exercise. Since neither the method of Fick nor the indicator dilution technique of measuring cardiac output can be applied during rapidly changing states, it has been necessary to delay such measurements after the onset of exercise until a "steady state" of cardiac output has been achieved. If the exercise is submaximal, of constant load and abrupt onset, an approximately steady state of oxygen consumption, arterial and venous oxygen content, heart rate, and ventilation is achieved after 1½ to 3 minutes of exercise.

Therefore, the determination of cardiac output is usually made during the fourth or fifth minutes of exercise. It is apparent that if the "response time" or rate of increase of the cardiac output during exercise varies under different conditions or in subjects with different types or degrees of severity of heart disease, such steady-state measurements might lead to an erroneous impression of the state of the circulation. It is conceivable that two individuals carrying out identical exercise in terms of severity and duration might

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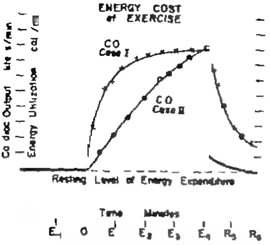

Fig. 1. The concept of the total cardiac output response to exercise of constant severity and abrupt onset and offset is shown. The heavy black line represents the level of energy expenditure by the body. At time O the rate of energy expenditure is increased abruptly by exercise of constant severity. At time E the exercise is abruptly terminated. The X——X line (Case 1) represents one possible pattern of response of cardiac output to such exercise. The O——O line represents another possible time course of cardiac output response. The total cardiac output of the two cases as reflected by the area enclosed by the two curves is greatly different although the cardiac output during the fourth minute is the same for both cases.

have an identical cardiac output during the fourth or fifth minutes of exercise. It is also conceivable that one of the subjects might achieve this level of cardiac *output within a very few seconds after* the onset of exercise and sustain it throughout the entire period of the exercise. The other might have a very gradual increase in the cardiac output such that if the cardiac output could be measured with precision during the first three minutes of exercise, considerably lower values would be obtained. If such variations exist it is apparent that the total cardiac output response of the two subjects would be grossly different even though their steady state values are identical. These concepts are illustrated in Fig. 1.

Since it is now possible to determine accurately cardiac output for each systole by a computer technique as previously described in this laboratory, it is possible to determine the time–cardiac output curve during exercise.[3] The accuracy of the method during unsteady states has been demonstrated in previous studies from this laboratory and others.[3,4] The present study was designed specifically to examine the concepts illustrated in Fig. 1.

Methods

A total of 34 subjects have been studied. 16 were normal subjects without evidence of hemodynamically significant heart disease. 9 were *patients without shunts who* were found to have a low cardiac output during exercise by the criteria of Donald and colleagues,[1] and 9 were patients with demonstrated heart disease but with normal cardiac output response during steady state exercise. Diagnoses of the latter two groups of patients are shown in *Table I*. By standard clinical criteria five of the low-output group were considered to be in functional Class II and four in Class III (New York Heart Association). Of the patients with a normal cardiac output three were considered Class I and five Class II.

All subjects were exercised in the supine position for 4 minutes using an electronically loaded bicycle ergometer.* The exercise was of constant load and abrupt onset. The degree of exercise was adjusted according to the previously determined tolerance of each patient to insure completion of the 4 minute exercise period. A catheter was placed in the superior vena cava or *pulmonary artery for* prompt venous access. A No. 5 Teflon catheter was introduced percutaneously and the tip advanced into the ascending aorta. The pressure was sensed with a Statham P23G manometer. The catheter manometer system was optimally damped mechanically as previously described. Determinations of cardiac output were made prior to exercise and between the third and fourth minutes of exercise with *either the standard* Fick or indocyanine dye dilution technique. Expired air was collected into a Douglas bag for 3 minutes during the preexercise period and between the third and *fourth* minutes of exercise *for minute* oxygen consumption determination. For determinations by the Fick method the

*Elema, Stockholm Sweden.

Table I

Pt. N	Age (yr.)	Sex	Diagnosis	Functional class*	Resting C.I. (L./min./M²)	Exercise $\dot{V}O_2$ (L./min./M²)	Exercise C.I. (L./min./M²)
A Patients with low three to four minute exercise cardiac index							
1	32	M	MS	III	2 53	478	4 33
2	26	M	MI and AS	II	1 52	375	2 38
3	35	F	MS	III	2 68	300	3 80
4	31	M	MS	III	2 38	588	4 49
5	24	F	MI	II	2 21	369	4 08
6	28	M	MS	II	3 15	432	4 70
7	30	F	MS	II	2 93	340	4 05
8	46	M	AS	III	2 49	505	4 75
9	22	F	MS	II	3 02	368	4 35
B Patients with normal three to four minute cardiac index							
1	36	M	AS	II	2 61	570	5 89
2	34	F	AS and MS	II	4 19	425	5 95
3	21	M	Pul. stenosis	II	4 62	354	5 82
4	28	F	HSAS†	II	3 20	597	6 17
5	41	F	MS	II	3 66	341	5 84
6	40	M	ASHD	II	3 96	593	6 35
7	48	M	HSAS†	I	2 87	496	3 61
8	26	F	MS	II	4 05	492	6 50
9	24	F	MS	III	2 97	315	4 57

*New York Heart Association Classification.
†Hypertrophic subaortic stenosis on treatment (Reserpine).
C.I. Cardiac index, i.e., cardiac output per square meter of body surface area. $\dot{V}O_2$ oxygen consumption.

blood O_2 content was measured in duplicate with the Van Slyke apparatus. Oxygen and CO_2 content of the expired gas was measured with the Scholander microgasometer.

Throughout the period of study the linear blood flow velocity in the ascending aorta was computed. The time derivative of the aortic pressure was used as the input to an electronic circuit providing a solution of a modification of the Navier-Stokes equation describing flow in distensible tubes.[4-6] The proportionality constant necessary to express the computed velocity of flow as stroke volume was derived by comparison of the integral of the velocity curves in systole, with the stroke volume obtained at rest by Fick or dye dilution technique. This method has been subjected to extensive experimental validation in animals. A recent reported study in man demonstrated a correlation coefficient of 0 90 with 72 points of comparison between such computed cardiac outputs and those obtained by Fick or dye dilution technique.[3] In the study herein reported the computed stroke volume was calibrated at rest from simultaneously measured Fick or dye dilution cardiac outputs. The computed stroke volume was then measured at 30 second intervals during the 4 minutes of exercise. Ten consecutive velocity curves were integrated and the average value multiplied by the heart rate and by the calibration factor to yield the cardiac output at each interval of exercise. A comparison was made between the fourth minute of exercise dye dilution or Fick cardiac output and the cardiac output obtained simultaneously from the product of computed stroke volume and heart rate. No subject was included in the analysis unless the computed output was within 20 per cent of that of the Fick or indicator output measured during this period of steady state exercise. Three subjects were eliminated from this study by this criterion. The relationship between the computed and measured value is shown in Fig. 2.

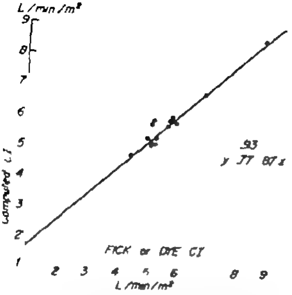

Fig. 2. Comparison of the Fick or Dye Dilution Cardiac Index values obtained in steady-state exercise with the values obtained by analogue computation from the ascending aortic pressure. These are values obtained from subjects in this study.

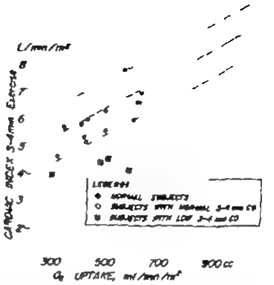

Fig. 3. The regression line and two standard deviation lines of the normal relationship between $\dot{V}O_2$ and steady-state cardiac index is shown. The regression equation is $CI = 3.7 + 0.00553\ \dot{V}O_2$ (Donald and associates[1]). The steady-state exercise values from the subjects used in this study are plotted. One of the normal subjects has a value below the predicted range. For purposes of the study the patients were divided in two categories, those with steady-state output below the predicted range and those below it.

For the 34 exercise values of the subjects retained for analysis, the standard error of the computed estimate is 0.47 L. per minute per square meter.

Results

During the third to fourth minute of exercise, the oxygen consumption of the normal subjects averaged 550 ml. per minute per square meter (range 380 to 933 ml. per minute per square meter), the low cardiac output group had an oxygen consumption averaging 417 ml. per minute per square meter (range 300 to 588 ml. per minute per square meter) and the normal output patients had an uptake of 464 ml. per minute per square meter (range 315 to 597 ml. per minute per square meter).

The computed cardiac output and oxygen uptake during the fourth minute of exercise is shown in Fig. 3. Cardiac output averaged 6.1 L. per minute per square meter for the normal subjects and 4.1 L. per minute per square meter for the patients with subnormal steady state output. All but one of the values of the normal subjects fell within the 90 per cent confidence limits for normal subjects established by Donald and colleagues[1] for the relationship between oxygen consumption and cardiac output. By definition the values of all of the subjects with low outputs fell below the predicted range. However, some of the differences between normal and abnormal are very slight.

The average heart rate of the normal subjects during the last minute of exercise was 117 beats per minute (range 74 to 164 beats per minute), of those in the low output group 126 beats per minute (range 105 to 150 beats per minute), and of those in the normal output group 120 beats per minute (range 91 to 153 beats per minute). If heart rate can be taken as an index of relative stress, then it is apparent that *the patients with heart disease were stressed* slightly more than the normal subjects even though the oxygen consumption and cardiac output were less in the latter group.

The heart rate, stroke index, and cardiac output during each of the periods of measurement are considered as a percentage of the fourth minute response. That is

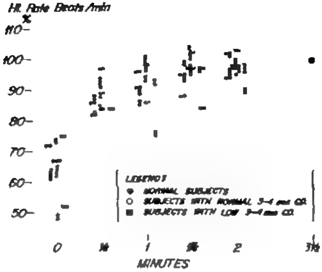

Fig. 4 The heart rate is plotted at ½ minute intervals as a function of time. The rate has been nondimensionalized so that the 3½ minute steady exercise response is 100 per cent and earlier rates are compared to this as percentage

the value obtained during the third to fourth minute of exercise is considered to be 100 per cent and preceding values are expressed relative to this. For this calculation the computed cardiac and stroke index were used. The heart rate response, considered in this manner, is illustrated in Fig. 4. The rate at 3½ minutes of exercise is by definition 100 per cent. When the rate response is considered at 30 second intervals, it is apparent that all three groups have a rapid increase in the first 30 seconds. The normal subjects have achieved approximately 90 per cent of their final heart rate at ½ minute. The group with the final low output are somewhat lower with an average increase to 82.6 per cent of the final output. This difference is not significant. There is a considerable individual range in the resting heart rates although each of the three groups averaged approximately 65 per cent of their final exercise value.

Stroke index may be considered in the same manner. Some patients and normal subjects maintained unchanged stroke volume throughout the exercise period. Others increased the stroke volume and some actually decreased the stroke volume with exercise. Although the patients with low 3 to 4 minute exercise outputs had resting stroke volumes somewhat lower than the control subjects, the changes with exercise are variable. No consistent pattern was observed.

The time course of cardiac output in response to a 4 minute exercise period is illustrated in Fig. 5. There is a moderate scatter of resting values when the resting output is considered as a percentage of the final cardiac output. A moderate separation of the normal group from the patients with a final low cardiac output is apparent at ½ minute. The normal controls achieved an average of 88.4 per cent of their final cardiac outputs at ½ minute. The patients with low cardiac outputs averaged 77.9 per cent of the final value. This difference is significant (t = 3.12). The difference is still apparent at 1 minute of exercise but is less obvious at 1½ and 2 minutes. The values obtained from patients with normal steady state cardiac outputs range between the values for the normal subjects and those with subnormal steady state cardiac outputs.

Discussion

These findings suggest that subjects with a subnormal cardiac output during the steady-state phase of exercise also have a tendency to reach their peak cardiac output slowly. If this is true, then the addition of the cardiac output values during

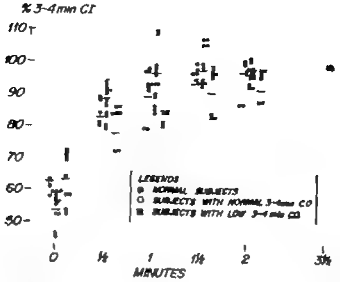

Fig. 5. The cardiac index considered as a percentage of the three to four minute output plotted as a function of time. The three groups of subjects are distinguished as in previous figures. The average value of each group is indicated by a horizontal bar. There is significant separation of the normal subjects and the patients with low steady-state output at ½ and 1 minute.

all four minutes of exercise should clearly separate the normal and subnormal subjects. To examine this possibility the cardiac output during the entire 4 minutes was cumulated and expressed as liters per square meter of body surface area. The total output was obtained by cumulating the ½ minute cardiac output values. These are plotted in Fig. 6 as a function of oxygen consumption during the fourth minute of exercise. This minute oxygen uptake is taken to represent the severity of exercise. A striking separation is achieved between the patients with final low cardiac output and the normal subjects. Regardless of exercise level all of the normal subjects had a total four minute output of greater than 20 L. per square meter of body surface area. In contrast the subjects with low final cardiac outputs achieved a maximum of 17½ L. per square meter total output, although there is a considerable overlap of the values of oxygen consumption. The separation between the normal and abnormal groups shown in Fig. 6 is similar to that obtained with the Donald regression (Fig. 1). However the cumulative approach increased the separation appreciably.

The one normal subject who had a low 3 to 4 minute output is well within the normal group when his output is considered for the entire four minutes. This individual with an oxygen consumption of 471 ml. per minute per square meter had a cumulative output of 21.8 L. per square meter.

There is considerable scatter of the cumulative output measured from the patients with definite heart disease but normal fourth minute cardiac output. One subject despite a normal final output had a low cumulative output placing her within the abnormal group. This individual was quite symptomatic with a history of marked decrease in exercise tolerance and findings of severe mitral stenosis. The normal steady state output was surprising.

It was anticipated that the rate of increase of cardiac output with exercise would be a function to a considerable extent of the level of exercise.[7] When the normal subjects in this series are considered in terms of exercise level they may be divided into those with an oxygen consumption during the 3 to 4 minute period greater than 500 ml. per minute per square meter and those with less than this. Considered in this way the percentage of final response at ½ minute and at 1 minute show considerable overlap not supporting the postulate. The eight subjects with a $\dot{V}\ O_2$ (oxygen consumption per minute) less than 500 ml. per minute per square

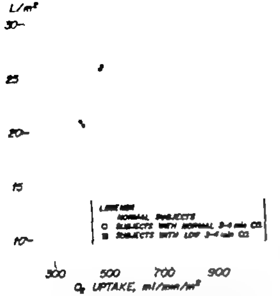

Fig. 6. The total cumulated cardiac output is plotted against the work level (steady-state $\dot{V}O_2$). All work loads were steady with abrupt onset and exactly four minutes duration. Subject type symbols are constant in all slides.

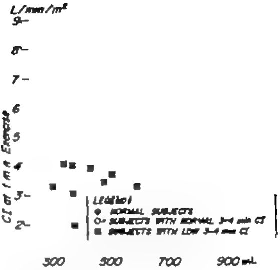

Fig. 7. Cardiac index at one minute is plotted against steady state O_2 consumption is expressed in ml. per minute per square meter.

meter had achieved 89.9 per cent (SD 5.6 per cent) at one-half minute and 99.8 per cent (SD 9.0 per cent) at one minute. The eight subjects with $\dot{V}O_2$ greater than 500 ml. per minute per square meter had outputs of 86.9 per cent (SD 8.5 per cent) at ½ minute and 93.4 per cent (SD 9.7 per cent) at one minute. These small differences in the two groups are not significant. However, few of the exercise levels were sufficiently high and the total number is inadequate for final conclusion about this point.

It is apparent that considerable information may be obtained about patients if the first minute of exercise alone is considered. The exercise level as determined by the fourth minute oxygen consumption has been plotted against cardiac output at one minute of exercise (Fig. 7). At this level there is already excellent separation between the normal and abnormal groups. This approach has obvious potential usefulness in the study of subjects who are unable to sustain a given exercise level for standard testing.

The slow response time of the patients with subnormal steady-state cardiac output response to exercise is of particular interest. Such a response would be anticipated in a controlled system. The circulatory stimulus arising from an inadequate cardiac output would be increasing during the early phases of exercise, tending to produce a greater response during the succeeding periods. A low initial output could be expected to produce a greater circulatory stimulus leading toward a greater response. The longer the cardiac output remained suboptimal but less than maximum, the longer will be the period required to achieve a steady state.

None of the subjects in this study showed an overshoot (initial response greater than steady state) of either the heart rate or cardiac output. This finding in man is in contrast to the response of the intact dogs studied by Franklin and co-workers. In such animals, the steady values are frequently exceeded by significant amounts during the first half minute of exercise. It has not been established clearly whether such responses are primarily anticipatory (psychologic) or whether they are due to physiologic influences. This lack of overshoot in man has been previously noted by Cerretelli and associates and by Gilbert and co-workers.

Summary

Cardiac output was monitored continuously during 4 minutes of steady state exercise in 34 human subjects, of whom 16 were normal volunteers 9 had heart disease with a cardiac index within normal limits during the fourth minute of exercise and 9 had subnormal levels of cardiac output during the same period of timed exercise The linear flow velocity in the ascending aorta was computed using the time derivative of the aortic pressure as the input to a circuit providing approximate solution to a modification of the Navier-Stokes equation The proportionality constant necessary to express the output as volume flow was derived by comparison of the integral of the flow curves in systole with a simultaneously determined cardiac output by the Fick or dye dilution methods with the subject at rest.

The cardiac output was examined each 30 seconds throughout the 4 minute period of exercise as a percentage of the level attained during the fourth minute Striking differences between the three groups were seen 30 seconds after the start of exercise. The normal subjects had achieved 88 4 per cent of the maximal level at 30 seconds The patients with a subnormal steady-state cardiac output had achieved only 77 9 per cent of their final value at this time while the patients with normal steady state levels were intermediate at 30 seconds. The differences in the groups were still present but diminished at one and two minutes of exercise.

The output was cumulated for the entire four minute exercise period in each patient and plotted as a function of work load (i.e. 3 to 4 minute V O_2) Considered in this manner a wide separation of the patients with low steady-state cardiac output and the normal subjects was achieved without overlap

These data suggest that patients with a subnormal cardiac output during the steady state phase of exercise tend to increase their cardiac outputs more slowly in response to a given exercise than do normal subjects or patients with less severe heart disease.

REFERENCES

1 Donald, K. W Bishop, J M Cumming G., and Wade O L. Effect of exercise on the cardiac output and circulatory dynamics of normal subjects, Clin. Sc. 14:55 1955
2 Ekelund, L. G., and Holmgren, A. Central hemodynamics during exercise, Circulation Res. (Suppl. I) 20 1 1967
3 Jones, W B Russell, R. O Jr and Dalton, D H., J A evaluation of computed stroke volume in man, Am. Heart J 72 746, 1966.
4 Jones, W B., Hefner L. L Bancroft, W H., J and Klip, W Velocity of blood flow and stroke volume obtained from the pressure pulse J Clin. Invest. 38:2087 1959
5 Jones, W B., and Griffin, J B Comparison of computed aortic blood velocity with that of electromagnetic flowmeter J Appl. Physiol. 17:482, 1962.
6. Greenfield, J F Jr Patel, D J Barnett, G. O and Fox, S. M III Evaluation of the pressure time derivative method for estimating peak blood flow Am. Heart J 63 101 1962.
7 Astrand, P O and Saltin B. Oxygen uptake during the first minutes of heavy muscular exercise, J Appl. Physiol. 16:971 1961
8. Franklin, D L., Ellis, R. M and Rushmer R. F Aortic blood flow in dogs during treadmill exercise, J Appl. Physiol. 14:809 1959
9 Cerretelli, P Sikand, R., and Farhi, L. E. Readjustment in cardiac output and gas exchange during onset of exercise and recovery J Appl. Physiol. 21 1345 1966.
10. Gilbert, R., Auchincloss, J H J and Baule, G H Metabolic and circulatory adjustments to unsteady state exercise, J Appl. Physiol. 22:905 1967

The T loop in right bundle branch block

A vectorcardiographic study of 82 cases

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Vectorcardiographic studies of QRS loops in right bundle branch block (RBBB) have been reported by many authors, and the classic abnormalities are discussed in texts and symposium proceedings.[1-4] The T loop in RBBB has received scant attention thus far except for Chou and associates[5] who reported the incidence of abnormal T loop wideness in 10 per cent of RBBB cases. The rotational characteristics of T loops in RBBB as encountered in ischemic heart disease, in right ventricular enlargement, and in healthy persons have not been explored.

The purpose of this investigation was to survey T loop characteristics in a series of patients whose RBBB was of diverse etiology.

Materials and methods

The files of the Electrocardiogram (ECG) Departments of four hospitals were surveyed for cases of RBBB. Cases were admitted to the study if the T-loop inscriptions permitted accurate measurement of direction and rotation in three reference planes. In all, 82[1] such examples were found. The QRS interval in each was at least 100 msec. with a terminal appendage, or terminal delay, oriented to the right. Frank system vectorcardiograms (VCG's) were displayed by means of a Sanborn vector amplifier and Viscoscope and photographed on 3,000 ASA Polaroid film. Time dashes for T-loop study were set at 10 msec. and high amplification was used.

In each case, the direction and rotation of the body and appendage of the QRS loop was determined for each reference plane. In the right ventricular enlargement group, the direction of instantaneous vectors at 30 and 40 msec. from QRS onset were also plotted for the three planes. T direction and T loop length and width were measured in the three planes by the method of Helm. The sagittal plane was viewed from the right. The maximum T length in any plane divided by the maximum width gave the spatial length/width (L/W) ratio. The rotation of T loops in each

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plane was recorded as clockwise (CW) or counterclockwise (CCW). When the spatial T loop L/W ratio was eight or more indicating an elongated slender loop, the rotation could not be determined and the loop was designated as narrow (N).

Normals (*19 cases*). These individuals had no clinical or radiological evidence of heart disease. They had been hospitalized for noncardiac problems or had undergone a routine annual physical examination with normal results except for RBBB.

Right ventricular hypertrophy (*17 cases*). These patients were all hospitalized for cardiac or cardiopulmonary disease. In 11 cases, the diagnosis could be considered "certain RVE" because of catheterization or surgical data. In the remaining 6 "possible RVE" cases, RVE was considered because of the clinical situation (asthma,

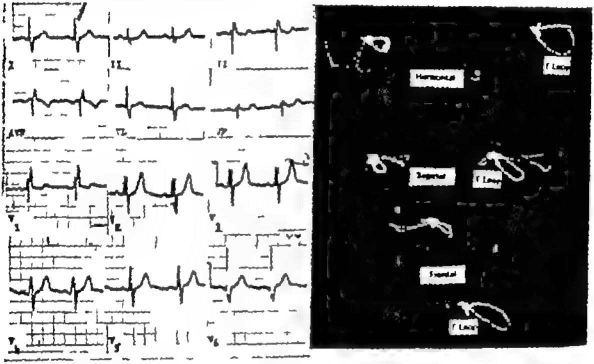

Fig. 1. Scalar electrocardiograph and vectorcardiograph of a 25-year-old man with RBBB and no evidence of heart disease. Note the CW rotation of the T loop in the horizontal and frontal projections and CCW rotation in the sagittal plane.

Table I. Loop rotation in RBBB

	Horizontal						*Right sagittal*	
	Body QRS		*Appendage*		*T loop*		*Body QRS*	
	CW	CCW	CW	CCW	CW	CCW	CW	CCW
No heart disease (19)	1	18	10	8	13	2	13	4
Ischemic (13)	2	12	1	13	10	1	7	7
Right ventricular enlargement (17)	6	11	5	12	11	1	11	5
Anterior infarction (11)	9	2	5	5	5	1	9	2
Inferior infarction (20)	4	18	8	10	12	8	11	5

emphysema pulmonary emboli or small atrial septal defect) but was not proved by operation or physiological data.

Myocardial infarction (31 cases) In these patients the *initial QRS forces* were grossly abnormal[1,4] and the clinical picture was that of myocardial infarction. In 20 cases, the 30 msec. vector was superior (inferior infarction) Included in the group were several instances of markedly increased anterior QRS voltage probably reflecting dorsal infarction as well.[9] In 11 cases, initially posterior or right and posterior QRS forces identified anterior or anterolateral infarction

Ischemic heart disease (14 cases) These patients had all been hospitalized for coronary disease, coronary insufficiency or congestive heart failure. Cases were not excluded because of hypertension or cardiac enlargement. However in all, the QRS loops of RBBB did not present the initial deformities of myocardial infarction.

The obtained data for the direction and rotation of QRS loops, appendages, and T loops, as well as for T-loop length width and L/W ratio were assembled in diagrammatic and tabular form. The data for the several groups were compared using the chi square test, Fisher s exact probability test, Student s t test, and Mann-Whitney U test.

Results

RBBB without clinical heart disease RBBB in patients without clinical heart disease, presents characteristic but not invariable QRS and T loops. The QRS body is oriented left and posterior with CCW rotation The appendage is rightwards and usually anterior and may rotate CW or CCW

The T loop (Fig 1 Tables I and II) in the horizontal plane is directed to the left and slightly anterior or posterior to the X axis. The T loop rotation in this plane was typically CW In the right sagittal view the QRS body is posterior and clockwise, the appendage anterior but of variable rotation. The T loop in this projection usually rotates in a CCW manner and is markedly inferior

Viewed in the frontal plane, the T loop was *always CW or narrow The body and* appendage were variable

The data for T loop direction length and wideness in the three reference planes are presented in Table *II* The mean spatial L/W ratio was 4 9

Fig 1 the ECG and VCG of a 25-year old man illustrates these points.

Right ventricular enlargement In general the QRS and T loops in RBBB with RVE were similar to those of RBBB without heart disease. However certain differences were apparent on inspection of the data and were confirmed by statistical tests.

QRS BODY The incidence of CW horizontal loops (6 of 17 cases) greatly exceeded the incidence in normals (1 of 19) confirming the observations of Walsh The location of the 30 and 40 msec. instantaneous vectors was plotted for the RVE certain and "possible groups as well as for the normals (Table IV) In our material the 30 and especially the 40 msec. QRS vectors

plane				*Frontal plane*					
Appendage		*T loop*		*Body QRS*		*Appendage*		*T loop*	
CW	*CCW*	*CW*	*CCW*	*CW*	[illegible]	*CW*	*CCW*	*CW*	*CCW*
6	6	4	7	9	9	9	5	8	0
4	7	8	7	3	12	4	10	10	2
6	10	1	18	9	7	12	5	6	3
6	1	2	0	5	6	4	6	3	0
4	9	5	7	11	9	11	4	10	4

Table II T-loop characteristics

	T direction		T voltage		Width		L/W	
	Mean	*S.D*	*Mean*	*S.D*	*Mean*	*S.D*	*Mean*	*S.D*
Horizontal	356.8	24	0.43	±0.13	0.13	±0.07	4.2	±1.8
Sagittal	82.3	33	0.30	±0.15	0.12	±0.08	3.5	±1.6
Frontal	26.3	11.0	0.50	±0.20	0.09	±0.09	5.0	±1.8
Maximum for all planes			0.52	±0.19	0.13	±0.09	4.9	±3.0

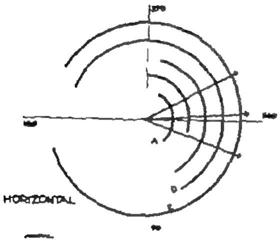

Fig. 2. Range of T loop direction in the horizontal plane for five clinical groups of RBBB. The double-headed arrow indicates the mean direction for cases without clinical heart disease. *A*. The single-headed arrows indicate one standard deviation in this group. *B*, right ventricular enlargement. *C*, clinical ischemic heart disease. *D*, anterior infarction. *E*, inferoposterior infarction.

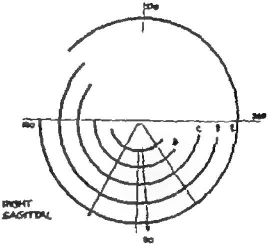

Fig. 3. Range of T-loop direction in the right sagittal plane for five clinical groups of RBBB. The double-headed arrow indicates the mean deviation for cases without clinical heart disease. *A*. The single-headed arrow indicate one standard deviation in this group. *B*, right ventricular enlargement. *C*, clinical ischemic heart disease. *D*, anterior infarction. *E*, inferoposterior infarction.

were deviated markedly from similar vectors in RBBB without heart disease. In the "certain RVE" group, for example, in only three of ten cases was the 40 msec. vector left and posterior. In the other seven instances the 40 msec. vector was either anterior and left or deviated to the right.

The T loop rotations in RBBB with RVE, CW in the horizontal and CCW in the right sagittal, were similar to the rotation in RBBB without heart disease (Table I). However, the direction of T was considerably posterior (Figs. 2, 3, and 4) in the RBBB plus RVE group and this difference was statistically significant at the 1 per cent level.

The spatial L/W ratios of the T loops in RBBB and RVE were normal (greater than 2.6) in 12 of 16 cases (Table IV). Thus, abnormal wideness was observed in only 25 per cent. Indeed, L/W ratios of eight or more were noted in nine of sixteen cases.

The findings in RVE with RBBB are illustrated in Figs. 5 and 6 which present the ECG and VCG of a 12 year-old boy with Fallot's tetralogy before and after RBBB which first occurred during surgical correction.

Inferior posterior infarction. It was anticipated that the direction of T in RBBB with inferior posterior infarction would be significantly more superior than in RBBB

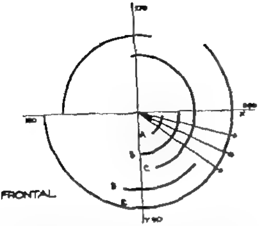

Fig. 4. Range of T-loop direction in the frontal plane for five clinical groups of RBBB. The double-headed arrow indicates the mean deviation for cases without clinical heart disease. *A*. The single-headed arrow indicates one standard deviation in this group. *B*, right ventricular enlargement. *C*, clinical ischemic heart disease. *D*, anterior infarction. *E*, inferoposterior infarction.

without heart disease.[14] This was true in several instances, but when statistical study and comparison with a variety of tests were done, no significant difference appeared in the T direction in the three reference planes between RBBB cases with inferior infarction and those without heart disease.

In 8 of 20 cases in this group, the spatial L/W ratio was less than 2.6. This was the highest incidence of abnormally wide T loops for a category studied (Table IV).

The rotation of T loops in RBBB with inferior infarction was CCW in the horizontal plane in 8 of 18 cases, representing a marked variation from uncomplicated RBBB. Similarly, CW T loops were seen in 5 of 12 in the right sagittal projection (the remainder were narrow).

Fig. 7 presents the ECG and VCG of a 71-year-old patient with dorsal infarction, inferior ischemia, and RBBB. The horizontal T loop, although left and anterior in position, exhibits CCW rotation. This unusual rotation for the horizontal T loop in RBBB was observed in 8 of 20 cases in this group (40 per cent).

Anterior infarction. The T loop direction in anterior infarction with RBBB was markedly right and posterior. The wide ranges observed are displayed in Figs. 2, 3, and 4. A very striking characteristic of T loops in this group was extreme narrowness, making determination of rotation impossible in many instances, especially in the sagittal and frontal planes (Table I). However, 4 of 11 cases manifested L/W ratio of less than 2.6, so that the over-all incidence of wideness (36%) is about the same as in other categories (Tables III and IV).

Fig. 8 presents the electrocardiograph, vectorcardiograph, and orthogonal X,Y,Z leads in a 45-year-old man with anterior infarction. Note the narrow sagittal and frontal T loop, its deviation right and posterior, and the even velocity of inscription. This feature in ischemic T loops has been described by Castellanos and colleagues.

Ischemic heart disease. As might be expected, the T loops in RBBB and clinical ischemic heart disease, but without QRS evidence of infarction, were variable (Figs. 2, 3, and 4, and Tables I, III, and IV). Many T loops exhibited directional and rotational characteristics indistinguishable from normals with RBBB. In other cases marked posterior or anterior deviation suggested anterior or dorsal ischemia. Wideness in this ischemic group was observed in 4 of 16 cases—again very similar to the other subdivisions of RBBB. The rotation of T loops in this group was quite similar to that seen with uncomplicated RBBB.

Discussion

The T loop in RBBB, in the absence of heart disease, displays rotation in the horizontal and right sagittal plane the opposite to T loops in normal subjects without RBBB. Hoffman and co-workers have shown[10] for adults, that the normal T loop with rare exceptions is CCW in the horizontal and CW in the right sagittal and frontal planes. In children, however, as noted by Castellanos and Lemberg, CW rotation in the horizontal may be seen in 40 per cent, presumably because of the greater influence of the right ventricle. Indeed, in a study of T loops in RVE, Hamby and colleagues[2] have found that CW horizontal and CCW right sagittal T loop rotation is the common pattern. Thus, in uncomplicated RBBB, the reversal of

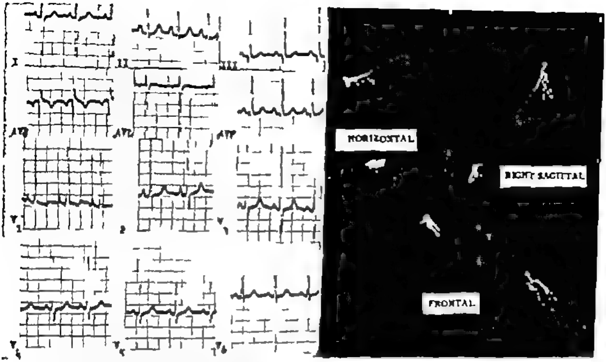

Fig 5 Scalar lectrocardiograph and vectorcardiograph of a 12 year-old boy with tetralogy of Fallot prior to surgery Note the absence of any delay in conduction. The QRS loop is oriented anteriorly and CW The T loop is to the left and somewhat *posterior and CW*

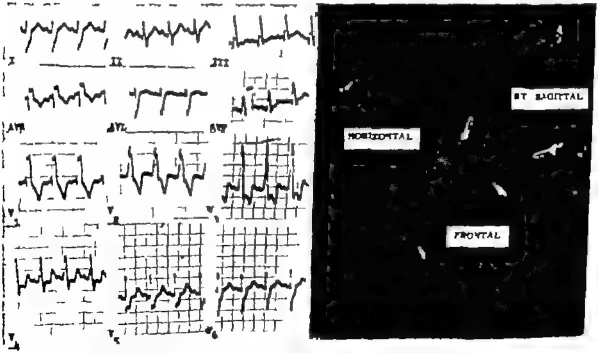

Fig 6 The scalar electrocardiograph and ectorcardiograph of the same patient as in Fig 2 after operation. Note the development of RBBB The QRS loop is somewhat more left and posterior in direction and the T loop is now much more posterior and of greater voltage but still demonstrates CW rotation in the horizontal plane.

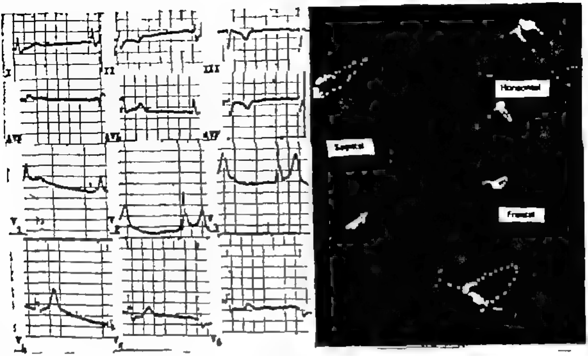

Fig. 7. Scalar electrocardiograph and vectorcardiograph of 71-year-old man with dorsal infarction and inferior ischemia and RBBB. The T loop in the horizontal projection, though left and anterior in direction, demonstrates CCW rotation.

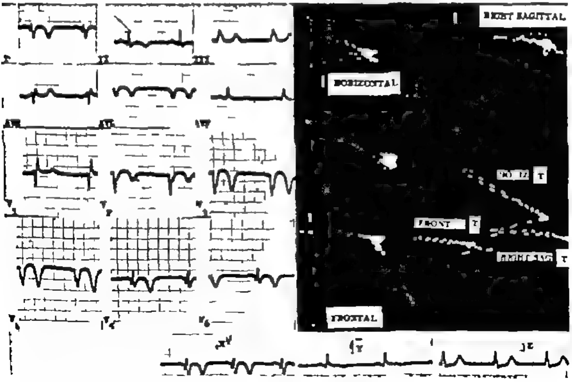

Fig. 8. Scalar electrocardiograph and vectorcardiograph and orthogonal X, Y, and Z leads in 45-year-old man with anterior wall infarction. T loop is located to the right and posterior and is very narrow in the frontal and sagittal projections. Note even velocity of inscription of the T loop as previously noted by Castellanos.

Table III. Planar and maximum T-loop voltage in RBBB

	Horizontal		Rt sagittal		Frontal		Mean maximum T length	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
No heart disease (19)	0.43	0.13	0.30	0.15	0.50	0.20	0.52	0.19
Right ventricular enlargement (17)	0.46	0.23	0.38	0.24	0.46	0.18	0.53	0.23
Ischemic heart disease (15)	0.59	0.27	0.62	0.46	0.64	0.31	0.78	0.43
Anterior infarction (11)	0.30	0.23	0.36	0.23	0.37	0.26	0.47	0.28
Inferior infarction (20)	0.41	0.26	0.33	0.15	0.36	0.17	0.48	0.22

Table IV. L/W ratios

	Spatial T loop L/W ratio		T loop with L/W ratio of 2.6	
	Mean	S.D.	N	Per cent
No heart disease (19)	4.9	3.0	4	21
Right ventricular enlargement (17)	7.8	4.0	2	12
Ischemic heart disease (15)	3.7	1.6	5	33
Anterior infarction (11)	8.6	8.8	4	36
Inferior infarction (20)	2.8	1.4	8	40

T loop rotation from normal closely resembles that seen in childhood or in RVE. It is important that the cardiologist interpreting the VCG's know the expected T direction and rotation in uncomplicated RBBB. He will then be able to detect deviations from this pattern which may point to cardiac disease.

T loop wideness, defined by Chou[15] as a spatial L/W ratio less than 2.6 was found in 25 per cent of RBBB cases without heart disease as compared with 5 per cent of normal subjects without RBBB. The data in Table II indicate mean T lengths quite equivalent to T length in normal patients without RBBB. Thus the high incidence of spatial wideness of the T loop was due to increased mean T width. Obviously, T loop wideness will be encountered often in uncomplicated RBBB and is not a reliable guide to pathology.

The T loop in right ventricular enlargement with RBBB is very similar to that seen in uncomplicated RBBB. The rotational characteristics and incidence of wideness are the same. However, the RBBB plus RVE T loops are more posteriorly directed. In an individual case this may be an unreliable clue to diagnosis, as the two groups overlap. Nevertheless, since only 3 of 19 cases of RBBB without heart disease had T loops at 315° or more posterior in the horizontal plane whereas 9 of 17 RVE-RBBB cases were so oriented, it would seem that in RBBB a T loop oriented at 315° or posterior provides a clue to the presence of RVE. This is particularly true if the L/W ratio is high, another characteristic of the T loop in the RVE group.

Although this RBBB study was oriented primarily to the T loop, an attempt was

made to find some QRS characteristics which might identify RVE cases not suggested by CW rotation of the QRS loop. Of many parameters measured the direction of the 40 msec. instantaneous vectors had the most value. This was either rightward or anterior in 7 of the 10 certain RVE cases, in sharp contrast to RBBB without heart disease. The posterior and rightward shift of the QRS body in RVE and RBBB seen in several cases resembles the findings in mitral stenosis[19] or emphysema[21] in which posterior shift of QRS loops also occurs.

The CCW rotation of T seen frequently in the horizontal plane with RBBB and inferior posterior infarction may prove to be a useful vectorcardiographic sign. Whether these T loops were oriented left and anterior or to the right of 180° CCW rotation was very frequent. This is in sharp contrast to the CW rotation of the left anterior T loop of RBBB without heart disease. It is also in contrast to the CW rotation often seen in ischemic T loops which are oriented anteriorly in the absence of RBBB. Thus in RBBB an anterior CCW rotating T loop should raise the question of myocardial ischemia probably dorsal in location. Since 2 of 19 normal subjects exhibited such rotation this sign will require cautious interpretation.

In anterior infarction with RBBB the T loop was deviated to the right and posteriorly. These right and posterior T loops generally exhibit CW rotation in the horizontal plane thus resembling similarly oriented ischemic T loops without RBBB.[22] In this position the angle formed by the QRS appendage and the T loop (both rightwards) will be narrow. This has been pointed out as a sign of myocardial disease in the presence of RBBB.[23] Spatial wideness was common in all coronary disease categories. The highest incidence (40 per cent) was in the inferior infarction group. However very narrow T loops were often encountered especially with anterior infarction. The mean spatial L/W ratio in this group was 8.6 the highest of any coronary disease category.

Summary and conclusions

1. T loop direction rotation and wideness were determined in 82 patients with RBBB.

2. Clockwise rotation in the horizontal plane and CCW in the right sagittal were observed in RBBB without heart disease and in RBBB with RVE.

3. In RVE with RBBB the T loop was more posterior than in RBBB without heart disease and displayed relatively high L/W ratios.

4. In inferior posterior infarction, the T loop often rotated CCW in the horizontal plane.

5. In anterior infarction the T loop was right and posterior and usually rotated CW in the horizontal plane.

6. The length width ratio of T loops in RBBB exceeded 2.6 in 25 to 40 per cent of all cases, regardless of etiology and is not a reliable guide to specific diagnosis.

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REFERENCES

1. Lasser, R. P., and Grishman, A.: Spatial vectorcardiography: right bundle branch block. VIII. Am. Heart J. 42:513, 1951.
2. Walsh, T. J.: A vectorcardiographic study of right bundle branch block with the Frank lead system and clinical correlation. Ventricular hypertrophies and chronic lung disease, Vectorcardiography 1965. Proceedings of The Long Island Jewish Hospital Symposium, 1966, North Holland Publishing, p. 137.
3. Scherlis, L., and Lee, Y. C.: Right bundle branch block following open heart surgery, Am. J. Cardiol. Vol. 8, 780, 1961.
4. Duncet, P., Walsh, T. J., and Massie, E. A.: Vectorcardiographic study of right bundle branch block with Frank lead system. Clinical correlation in myocardial infarction, Am. J. Cardiol. 16:342, 1965.
5. Braunwald, E., Donoso, E., Sapin, S. O., and Grishman, A.: Right bundle branch block, hemodynamic, vectorcardiographic, and electrocardiographic observations, Circulation 13: 866, 1956.
6. Scherlis, L., and Lee, Y. C.: Transient right bundle branch block: An electrocardiogram and vectorcardiographic study, Am. J. Cardiol. 11:173, 1963.
7. Frank, E. A.: accurate clinical practical system for spatial vectorcardiography, Circulation 13:737, 1956.
8. Massie, E., and Walsh, T. J.: Clinical vectorcardiography and electrocardiography, Chicago, 1960, Year Book Publisher, Inc., p. 265.
9. Blatem, A., Medrano, G. A., De Micheli, A., and Sodi-Pallares, D.: Experimental myocardial infarction in the presence of ... vectorcardiography 1965.

Island Jewish Hospital Symposium, 1966, North Holland Publishing Co., p 226.

10. Wolff R., and Gandhi, M J Posterobasal infarct, Vectorcardiography 1965 Proceedings of The Long Island Jewish Hospital Symposium 1966, North Holland Publishing Co. p. 201

11 Baydar I D Walsh T J and Massie E. A vectorcardiographic study of right bundle branch block with Frank lead system Clinical correlation in ventricular hypertrophy and chronic pulmonary disease Am. J Cardiol. 15 183, 1965

12. Donoso, E. Braunwald, E. Sapin, S O and Grishman, A. A study of electrocardiography and vectorcardiography in congestive heart disease, AM. HEART J 50:674 1955

13 Lee, Yu-Chen, and Scherlis, L. Some problems in the vectorcardiographic diagnosis of right ventricular hypertrophy Vectorcardiography 1965 Proceedings of The Long Island Jewish Hospital Symposium 1966, North Holland Publishing Co. p. 142.

14. Milnor W R. Electrocardiogram and vectorcardiogram in right ventricular hypertrophy and right bundle branch block, Circulation 16:348, 1957

15. Hoffman, I Taymor R C. and Kittel, I. T loop rotation in ischemic heart disease, Vectorcardiography 1965 Proceedings of The Long Island Jewish Hospital Symposium, 1966, North Holland Publishing Co., p. 181

16 Castellanos, A., Jr Lemberg, L., Salhaneck, L., and Gomez, A. The morphology of the ST T loop in healed myocardial infarction, Dis. Chest 50 113 1966.

17 Castellanos, A., Jr and Lemberg L. The T loop in ventricular enlargement in congestive heart disease, Vectorcardiography 1965 Proceedings of The Long Island Jewish Hospital Symposium, 1966, North Holland Publishing Co., p. 169

18. Hamby R., Hoffman, I and Glassman, E. T loop in R.V E., in press.

19 Chou, Te-Chuan, Helm, R., and Lach, R. The significance of a wide TSE loop, Circulation 30:400 1964

20. Taymor R. C., Hoffman, I and Henry E. The posterior QRS loop in mitral stenosis, Vectorcardiography 1965 Proceedings of The Long Island Jewish Hospital Symposium, 1966, North Holland Publishing Co., p. 147

21 Murata, K., Mitrushita, S., Kurihara, H., and Seki, M Some pitfalls of vectorcardiography diagnosis of myocardial infarction with particular respect to emphysema, Circulation 35 172, 1967

22. Henry E I Schack, J A., and Hoffman, I Significance of the relation of QRS and T waves in bundle branch block. A useful electrocardiographic sign, AM. HEART J 54:407 1957

Clinical and hemodynamic results of peritoneal dialysis for severe cardiac failure

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Heart failure, which is unresponsive to bed rest, low sodium diet, digitalis, and diuretics, is a most difficult therapeutic problem. Water restriction and acidifying regimens used to correct the commonly associated dilutional hyponatremia and hypochloremia are unpleasant, slow, and in our experience, often ineffective. Although the prognosis is usually poor, a remission may be of substantial duration if it can be produced. In addition, a temporary remission can lead to sustained improvement if it allows the patient to undergo healing of an acute process or to have a corrective operation.

Peritoneal dialysis provides a means to produce rapid changes in body water and electrolytes. Because of its minimal morbidity and the ease with which it can be used, it seemed to us to offer promise in the treatment of this often terminal phase of heart disease. In addition, early reports from other institutions have been favorable. Our study evaluated the effectiveness of peritoneal dialysis in the treatment of[1] severe and in some cases intractable, congestive heart failure.

Methods

A total of 16 patients are included in this report. Seven had rheumatic, three had hypertensive, and two had arteriosclerotic heart disease. One had constrictive pericarditis. Two were felt to have cardiomyopathy related to chronic alcoholism while the remaining patient had cardiomyopathy of an unknown cause. The patients were all extremely ill and several appeared moribund when dialysis was initiated.

Previous treatment included digitalis and a 0.5 to 1 Gm. sodium diet in all, mercurial diuretics in 14, chlorothiazide or hydrochlorothiazide in 9, ethacrynic acid in 3, spironolactone in 3, and furosemide in 1. Ammonium chloride was used in 7 and water intake was restricted in 5. Notwithstanding, none of the patients had shown improvement prior to the time of dialysis.

All dialyses were performed on the wards

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by members of the medical house staff using a previously described technique.[1] Commercially available dialysis equipment and solutions were used.* Two liter infusions were given alternating hypertonic (equal parts of 1.5 and 7 per cent dextrose) and isotonic (1.5 per cent dextrose) solutions. Potassium chloride (4 mEq. per liter) was added. The initial transmembrane exchange in peritoneal dialysis occurs between the peritoneal cavity and the intravascular volume; secondary exchanges occur between the intravascular and extracellular volumes, and the extracellular and intracellular volumes. It has been shown previously that equilibration of body water is slow in edematous, hyponatremic individuals with cardiac failure.[3] The use of the alternating tonicity of the dialysis fluid minimized the danger of excessive plasma volume depletion during the period of net water removal. Since the increase in total body water exceeds that of total body sodium in "dilutional hyponatremia" our primary goal was to remove more water than sodium. There is evidence that water equilibration between peritoneal dialysate and plasma is complete after 20 minutes, while the solute constituents do not achieve equilibrium until 2 hours or more. By limiting the equilibration time to 30 minutes or less maximum water exchange was obtained.

When possible dialysis was continued until the edema had disappeared or at least a 5 L. negative fluid balance was reached. Continuous observations were made with regard to dyspnea, râles, edema, systemic blood pressure, and mental confusion. The patients were weighed before and after 24 hours of dialysis and daily thereafter. Blood urea nitrogen (BUN), creatinine, and electrolytes were measured at the same intervals.† Total blood volume (TBV) and cardiac index (CI) were determined in some patients before dialysis, on the first day (after 24 hours of dialysis) and on the third day, using peripheral venous injection of radio-iodinated human serum albumin with precordial detection of the radiocardiogram and blood sampling after 15 minutes. These methods have been validated in patients with low cardiac output and heart failure.[4-7]

Results

Clinical response. The clinical findings are shown in Table I. The average fluid loss of the 16 patients was 6 L. and their weight declined an average of 5 kilograms during the period of dialysis. Most patients showed immediate improvement in the clinical manifestations of fluid overload. At the end of the dialysis, dyspnea was less in half of the 16 patients. Out of 11 patients, râles were fewer in 7. Edema decreased in all patients and cleared completely in two. A total of 15 patients had mental confusion of some degree prior to dialysis; this was much improved in most of them by the third day after dialysis.

The subsequent course in most patients treated was one of continued clinical improvement and fluid mobilization. This was evidenced by a further average decrease in weight of 4 kilograms from the end of dialysis until 2 weeks later in the 13 patients alive during that time. A total of 12 of the patients definitely entered periods of remission. Four of them improved sufficiently to undergo open-heart surgery. One of the four had triple valve replacement and is alive and working 18 months after dialysis. Another had triple valve replacement in April, 1967, and has had a satisfactory course since then. One underwent resection of a ventricular aneurysm and is now markedly improved 5 months after dialysis. The fourth died in the postoperative period after an operation for constrictive pericarditis. Five others left the hospital and enjoyed remissions of 2 to 16 months. In three others, remission lasted for just 3 weeks. The remaining four failed to gain remission or died within 3 days. One of them died of esophageal perforation on the third day, one died with cardiac arrhythmias on the second day, and one (L. S.) became hypotensive and oliguric and died on the second day. L. S. may have suffered from vascular volume depletion induced by dialysis; however, it should be noted that her blood volume decreased by 3.7 L. while that of K. B. who gained remission decreased by 4.2

*Peridial, Cutter Laboratories, Berkeley, Calif. and Dianeal, Travenol Laboratories, Morton Grove, Ill.
†Technicon AutoAnalyzer.

Table I

Patient	*Diagnosis*	*A saline fluid balance at dialysis (L.)*	*During first 24 hours: Weight loss (Kg.)*	*During first 24 hours: TBV decrease (L.)*	*Clinical course*
F. D.	Rheumatic	5.5	5.0	0.8	Steady improvement. Free of heart failure in 2 weeks. Sudden unexplained death in third week
E. H.	Alcoholic	7.0	8.0	1.9	Recovered. Left hospital. Subsequent exacerbations. Still living after 1½ years
K. B.	Rheumatic	6.0	8.0	4.2	Improved to undergo triple valve replacement. I good health at present after 1½ years
A. E.	Constrictive pericarditis	7.0	7.0	0.8	Improved to undergo heart surgery. Postoperative death
J. E.	Rheumatic	5.0	4.0	0.8	Recovered. Left hospital. Refused to take medicines. Died with exacerbation t 2 months
C. A.	Arteriosclerotic	6.0	5.0	1.1	Improved to have resection of ventricular aneurysm. Quite well currently 5 months after dialysis
A. H.	Rheumatic	2.0	3.0	0.3	No improvement. Died in heart failure at 3 weeks
L. S.	Cardiomyopathy	5.5	1.0	3.7	Died with hypotension and anuria on second day
M. W.	Rheumatic	7.0	9.0	—	Recovered, left hospital, had 4 months remission before death
E. J.	Hypertensive	7.5	4.0	—	After good initial response, died of esophageal perforation on third day
V. K.	Arteriosclerotic	3.5	1.0	—	Died of ventricular arrhythmia on second day after moderate improvement from heart failure
D. Q.	Alcoholic	5.5	6.0	—	Improved rapidly left hospital, and still well at four months
A. M.	Hypertensive	7.2	6.0	—	Rapid improvement. Left hospital. Still well 2 months later
L. E.	Rheumatic	8.0	8.0	—	Three eek remission, then exacerbation of heart failure
W. L.	Rheumatic	7.2	7.0	0.8	Improved to ha triple alve replacement and is having good postoperative course
El B.	Hypertensive	6.0	6.0	—	Three week remission, then exacerbation of heart failure

L. Furthermore, the lowest TBV reached in L. S. was 92 ml. per kilogram which is above normal for our laboratory. The fourth and last patient in the group not gaining remission failed to improve and died in heart failure in 3 weeks. No other hypotension or arrhythmia occurred.

Blood chemistry. The majority of patients had serum sodium and/or chloride levels which were initially low (Fig. 1). In general, higher levels were recorded after dialysis and were maintained for at least 2 weeks. The average serum sodium increased from 126 to 136 mEq. per liter and the chloride from 86 to 97 during the dialysis period. It may be meaningful that 3 of the 4 patients who died early or failed to improve had initial serum sodium levels under 120 mEq. per liter and chloride under 85 mEq. per liter.

The BUN was elevated (above 15 mg. per cent) in 15 of the 16 patients. Twenty-four hours after dialysis was started it was lower in 9, higher in 6, and unchanged in 1. The average changed from 47 to 35 mg. per cent. Creatinine was measured just before and after dialysis in 10 patients. The average fell from 2.3 to 1.9 mg. per cent. The BUN/creatinine ratio was approximately 20:1 initially, suggesting prerenal azotemia. The average serum bicarbonate and potassium levels, respectively, were 26 and 3.8 mEq. per liter before, and 28 and 3.9 mEq. per liter after dialysis.

Hemodynamic measurements. TBV was

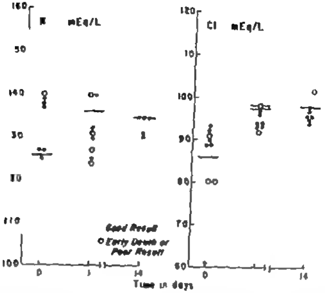

Fig 1 Serum sodium and chloride levels. Average values are represented by bars. There were 16 patients living at day 1 but only 13 at day 14 The average sodium level for those 13 on day 1 was the same as that for all 16. The higher average chloride value on day 1 is that of the 13 patients who were also studied on day 14

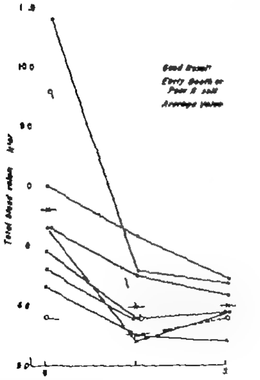

Fig 2 Total blood volume. Average values are represented by bars. Nine patients were studied on day 1 and 7 on day 3 The average values on day 1 of the 9 patients studied and of the 7 subsequently studied on day 3 were identical.

measured in nine patients with results as shown in Table I and Fig 2 It was markedly elevated in every patient prior to dialysis, ranging from 5 8 to 10 8 L. (110 to 159 ml per kilogram of dry weight) and averaging 7 6 L. (139 ml. per kilogram) The normal value for our laboratory is 74 ± 6 ml per kilogram (mean ± 1 S D) Dialysis caused a decrease in TBV in all the average falling to 6 0 L. (109 ml. per kilogram) after 24 hours and remaining essentially constant for 3 days. Seven of the 9 patients in whom TBV reduction was demonstrated gained remission. Another patient with marked reduction was the one mentioned previously whose death may have been related to excessive vascular volume depletion. The patient with the smallest decrease in TBV did not improve.

The CI was low initially in each of the 8 patients in whom it was measured (Fig 3) The average rose from 1 4 to 1 9 L. per *minute per square meter during* the first 24 hours (by the first day) of dialysis. The lower limit of the normal range in our laboratory is 2.5 L. per minute per square meter The six individuals in whom the CI increased with dialysis all entered a

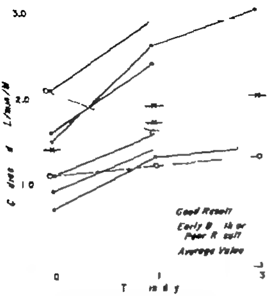

Fig. 3. Cardiac index. Average values are represented by bars. Eight patients were studied on day 1 and 6 on day 3. The lower average value on day 1 is that of the 6 also studied on day 3.

period of remission. The two in whom CI did not increase significantly are those mentioned above who did poorly despite a demonstrated reduction in TBV.

Case reports

Case 1. Patient K. B., 32-year-old man, had rheumatic fever at the age of 15 and began to have symptoms of heart failure at the age of 40. He had aortic and mitral stenosis and insufficiency. In spite of having stopped working 18 to 20 months ago, he was admitted to the hospital for heart failure twice within 2 months. The second time, he complained of dyspnea at rest and extreme fatigue, and exhibited râles and 3 plus sacral edema. He was treated with digitalis, hydrochlorothiazide, ammonium chloride, spironolactone, three injections of mercurial diuretics, morphine, a 1 Gm. salt diet, water restriction, and phlebotomy. During the next 7 days he lost only 2.7 kilograms, remained symptomatic and vomited frequently. His serum sodium was 127 mEq. per liter and serum chloride was 89 mEq. per liter. Peritoneal dialysis was then performed for 22 hours, with a net removal of 6 L. of fluid and a loss of 8 kilograms of weight. Edema was much less and râles were gone at the conclusion of dialysis. Within 2 days, he felt much better. In the next 2 weeks he lost 3 kilograms more and became edema free. The TBV changed from 10.8 to 6.5 L. and CI from 1.5 to 2.6 L. per minute per square meter during the dialysis period. Serum sodium and chloride levels at the end of dialysis were 130 and 94 mEq. per liter and 2 weeks later were 131 and 94. One month after dialysis, open-heart surgery was performed and the aortic, mitral, and tricuspid valves replaced with Starr-Edwards prostheses. There were no complications at surgery or in the immediate postoperative period. He was admitted with hepatitis 10 weeks later. This resolved and there were no other complications. He has improved continually and currently he is working half time as a barber 17 months after his operation.

Case 2. Patient C. A., a 62-year-old man, had a myocardial infarction 5 months ago and from the time of his hospital discharge had increasingly severe congestive heart failure. He was admitted to the hospital 3 months ago due to dyspnea uncontrolled by medications taken at home. He had pulmonary râles, a ventricular gallop rhythm, and ankle and sacral edema. He was treated with digitalis, bed rest, a 1 Gm. sodium diet, water restriction, chlorothiazide diuretics, furosemide, one injection of a mercurial diuretic, and oral ammonium chloride. During the next 2 weeks he lost 1.5 kilograms but his over-all condition had deteriorated. He was *lethargic, disoriented, fatigued, and more dyspneic.* Edema persisted. His serum sodium and chloride levels had gone from 134 and 97 to 125 and 93 mEq. per liter. He was felt to be moribund by those in attendance. Peritoneal dialysis was then performed for 40 hours with removal of 6 L. of fluid and loss of 5 kilograms of weight. Edema and râles were cleared rapidly and within three days he was better oriented and less dyspneic. TBV fell from 6.8 to 5.8 L. and CI rose from 0.7 to 1.3 L. per minute per square meter during dialysis. His serum sodium and chloride levels were 140 and 94 mEq. per liter at the end of dialysis and 143 and 100 two weeks later. His weight remained stable and he gained strength and claimed markedly less dyspnea over the next 2 weeks. During that time, a ventricular aneurysm was demonstrated angiographically. One month after dialysis it was resected without complication. He was feeling well when seen in the clinic 1 month later and was able to climb one flight of stairs without dyspnea.

Discussion

Severe heart failure often is associated with low serum levels of sodium and chloride.[8] The causative mechanisms are unclear but there is nearly always sodium overload with even greater water overload resulting in dilutional hyponatremia and hypochloremia.[12] Failure to respond to mercurial diuretics generally follows. Water restriction and acidifying regimens[1-17] have been used to correct the water and electrolyte abnormalities, but the former often causes overpowering thirst and the latter is slow and often limited by side effects and the risk of systemic acidosis.

Peritoneal dialysis provides a means of producing rapid changes in body water

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

to these patients while arranging equipment for peritoneal dialysis. A urine flow in excess of 200 ml. in the next hour would provide evidence that therapy with this diuretic agent probably would be successful. The absence of such an abrupt increase in urine flow in patients with refractory heart failure would be an indication to proceed with dialysis, since dialysis is capable of helping some patients who are severely ill with this syndrome.

Summary

A total of 16 patients with heart disease of various types underwent peritoneal dialysis for severe and often intractable cardiac failure. The average amount of fluid removed was 6 liters. Most patients had immediate improvement of symptoms and signs of fluid overload. 12 entered periods of remission, and four were improved enough to undergo corrective surgery with survival of three. An average weight loss of 6 kilograms occurred during dialysis and 4 kilograms more in the next 2 weeks. Serum sodium and chloride levels were depressed initially and returned toward normal in most patients. The average predialysis sodium and chloride levels were 126 and 86 mEq. per liter increasing to 136 and 97, respectively. Total blood volume (TBV) was greatly expanded beforehand and decreased with therapy in all 9 patients so studied. The average decrease was from 139 to 109 ml. per kilogram. Cardiac index (CI) was low in all and increased significantly in 6 of 8 patients so studied, the average changing from 1.4 to 1.9 L. per minute per square meter. The decrease in TBV, increase in CI, and sustained clinical improvement were closely associated. There were no definite complications, although in one instance excessive vascular volume depletion may have contributed to hypotension, oliguria, and death.

It is concluded that hypertonic peritoneal dialysis is an effective method for the treatment of severe heart failure with sodium dilution.

REFERENCES

1. Porter, G. A., and Starr, A.: Management of postoperative renal failure following cardiovascular surgery, Pacific Med. & Surg. In press.
2. O'Meara, M. P., Birkenfeld, L. W., Gotch, F. A., and Edelman, I. S.: The equilibration of radiosodium (Na^{24}), radiopotassium (K^{42}) and deuterium oxide (D_2O) in hydropenic human subjects, J. Clin. Invest. 36:784, 1957.
3. Boen, S. T.: Kinetics of peritoneal dialysis, Medicine 40:243, 1961.
4. MacIntyre, W. J., Pritchard, W. H., and Moir, T. W.: The determination of cardiac output by the dilution method without arterial sampling. I. Analytical concepts, Circulation 18:1139, 1958.
5. Schreiner, B. F., Jr., Lovejoy, F. W., Jr., and Yu, P. N.: Estimation of cardiac output from precordial dilution curves in patients with cardiopulmonary disease, Circulation Res. 7:595, 1959.
6. Kloster, F. E., Bristow, J. D., Starr, A., Mc Cord, C. W., and Griswold, H. E.: Serial cardiac output and blood volume studies following cardiac valve replacement, Circulation 33:528, 1966.
7. Schrieber, S. S., Bauman, A., Yalow, R. S., and Berson, S.: Blood volume alterations in congestive heart failure, J. Clin. Invest. 33:578, 1954.
8. Welt, L. G.: Edema and hyponatremia, Arch. Int. Med. 89:931, 1952.
9. Berliner, R. W., and Davidson, D. G.: Production of hypertonic urine in the absence of pituitary antidiuretic hormone, J. Clin. Invest. 36:1416, 1957.
10. Leaf, A., and Mamby, A. R.: An antidiuretic mechanism not regulated by extracellular fluid tonicity, J. Clin. Invest. 31:60, 1952.
11. Beren, B. A., Rokaw, S. N., and Masse, E.: Antidiuretic action of the urine of patients in cardiac failure, Circulation 2:409, 1950.
12. Weston, R. E., Grossman, J., Borun, E. R., and Hanenson, I. B.: The pathogenesis and treatment of hyponatremia in congestive heart failure, Am. J. Med. 25:558, 1958.
13. Bell, N. H., Schedl, H. P., and Bartter, F. C.: An explanation for abnormal water retention and hypo-osmolality in congestive heart failure, Am. J. Med. 36:351, 1964.
14. Rubin, A. L., Thompson, H. G., Jr., Braveman, W. S., and Luckey, E. H.: The management of refractory edema in heart failure, Ann. Int. Med. 42:358, 1955.
15. Ogden, D. A., Scherr, L., Spritz, N., Rubin, A. L., and Luckey, E. H.: The management of resistant fluid retention states with intravenous l-arginine monohydrochloride in combination with mercurial diuretics, Am. Heart J. 61:16, 1961.
16. Luckey, E. H., and Rubin, A. L.: The correction of hyponatremia in congestive heart failure, Circulation 21:229, 1960.
17. Mirgala, H. F., Laaser, R. P., and Friedberg, C. K.: The treatment of refractory retention of fluid with oral l-arginine monohydrochloride and meralluride, Am. Heart J. 65:5, 1963.
18. Burns, R. O., Henderson, L. W., Hager, A. B., and Merrill, J. P.: Peritoneal dialysis, New England J. Med. 267:1060, 1962.
19. Mailloux, L. U., Swartz, C. D., Onesti, G.

Heider C., Ramírez, O and Brest, A. N.: Peritoneal dialysis for refractory congestive heart failure J.A.M.A. 199:873, 1967
20. Nora, J J Trygstad, C. W., Mangos, J A., Gibbons, J E., and Jegier W Peritoneal dialysis in the treatment of intractable congestive heart failure of infancy and childhood, J Pediat. 68:693 1966.
21 Maher J F and Schreiner G. E. Hazards and complications of dialysis, New England J Med 273:370, 1965
22. Ross, J J and Braunwald, E. Studies on Starling's law of the heart IX. The effects of impeding venous return on performance of the normal and failing human left ventricle, Circulation 30 719 1964
23 Epstein, S E., Beiser G. D Stampfer M., and Braunwald, E. Depression of cardiac output at rest and during exercise produced by diuresis in patients with cardiac decompensation, Clin. Res. 15:200, 1967 (abstr.)
24 Katz, A. M The descending limb of the Starling curve and the failing heart, Circulation 32:871 1965.
25 Sarnoff S. J and Berglund, E. Ventricular function. I Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog Circulation 9 706, 1954.
26. Bennett, W H Van Rheenan, F J and Porter G A. Clinical effects of ethacrynic acid in patients with cardiac decompensation, Northwest Med. 67:31 1968.
27 Goldberg, M., McCurdy D K., Foltz, E. L., and Bluemle, L. W., Jr Effects of ethacrynic acid (a new saluretic agent) on renal diluting and concentrating mechanisms evidence for site of action in the loop of Henle, J Clin. Invest. 43:201 1964

The assessment of failure in aortic stenosis from the diastolic movements of the left ventricle

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During palpation of the cardiac apex in many patients with aortic stenosis, a small outward movement may be detected preceding the forceful systolic thrust of the hypertrophied left ventricle. Occasionally when the patient is in severe cardiac failure, an outward movement of the apex beat in early diastole coinciding in timing with a third heart sound is palpable. In the present study the abnormalities of the diastolic movements of the cardiac apex in aortic stenosis are analyzed and an attempt is made to relate the findings to the intracardiac pressures obtained during left heart catheterization.

For detailed analysis of the movements of the cardiac apex, the apexcardiogram was recorded in each patient using a displacement transducer held against the chest wall over the apex beat. The instrument used provides an accurate recording of the displacement of the cardiac apex relative to the thoracic wall and considerably extends the information obtained from clinical palpation of the apex beat.

Methods

The apexcardiogram was recorded from 20 patients with aortic valve stenosis. There were 15 male and 5 female patients, all over the age of 25 and all in sinus rhythm when the recording was made. Patients having evidence of mitral valve disease, either on clinical examination or at cardiac catheterization were excluded. A total of 21 subjects without evidence of heart disease ages ranging from 14 to 56 years, were also studied to establish normal values for the apexcardiogram using the present technique.

The apexcardiogram was recorded using a Philips inductive displacement transducer type PR9310 described as suitable for this work by Nixon and associates, and this instrument provided signals for direct application to an oscilloscope display and a galvanometer recorder. The transducer has a metal base and a protruding probe that is sensitive to movement along its long axis, the frequency response being flat from 0 to 50 c.p.s. The transducer was adapted for recording the apexcardiogram by placing an adjustable perspex cylinder over the base of the instrument so that the probe was nearly level with the open end of the cylinder.

The apexcardiogram was recorded with the patient lying on the left side and the breath held at the end of a normal expiration. An electrocardiogram (ECG) and a phonocardiogram from the left sternal edge were obtained simultaneously with the apexcardiogram and the tracings were recorded photographically using a multi

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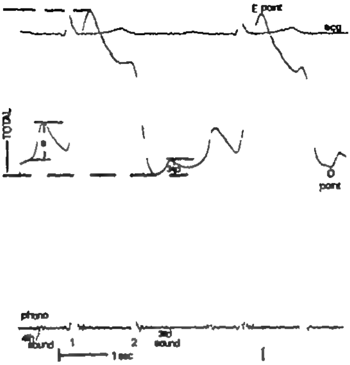

Fig. 1. Simultaneous recording of the apexcardiogram, ECG and phonocardiogram. The measurements made of the a wave and the third sound point are shown.

Fig. 2. Left ventricular diastolic pressure recorded from catheter in the left ventricle. Left atrial systolic pressure wave measured from Z point to A.

channel photographic recorder (New Electronics Products) at a paper speed of 80 mm per second

The presystolic wave of the apexcardiogram referred to as the a wave, was identified in each tracing as the positive deflection following the onset of the P wave of the ECG by an average of 0 11 sec.[8] and its height was measured from onset to peak (Fig 1) The third sound point when present, appears as the peak of the rapid filling wave in early ventricular diastole and the height of this point was expressed as the vertical distance between this point and the lowest point of the apexcardiogram the 0 point (Fig 1) The heights of the a wave and of the third sound point have been expressed as a percentage of the total amplitude of the tracing measured from the 0 point to the highest point during ventricular systole, thus allowing for differences in the amplitude of the apex cardiogram from one patient to another All reported ratios and measurements represent the mean of three consecutive cardiac cycles.

Pressure measurements were obtained from the left atrium and the left ventricle by trans-septal catheterization within five days of recording the apexcardiogram in all patients with aortic stenosis. For comparison with the apexcardiogram the left atrial systolic pressure wave and the left ventricular end-diastolic pressure were measured from recordings taken at a paper speed of 80 mm per second the left atrial systolic pressure wave being measured from the "z point to the peak of the left atrial a" wave, and the left ventricular end-diastolic pressure was taken at the point where the pressure rises abruptly at the onset of left ventricular systole (Fig 2) The measurements reported are the average measurements over one complete respiratory cycle Differences between the apexcardiogram in the normal group and the patients with aortic stenosis have been tested for significance by the t test and

Table I The normal apexcardiogram in 21 subjects with no evidence of heart disease

Subject	*Age*	*Sex*	*Diagnosis*	wave *Total amplitude (per cent)*
F S.	41	M	Cervical spondylosis	4 5
D D	19	M	Glandular fever	3 5
A. C.	56	M	Urethral fistula	9 0
R. C.	56	M	Duodenal lcer	7 0
D B	35	M	Ulcerativ colitis	7 0
D J	25	M	Normal	7 0
M J	20	M	Normal	7 5
J T	35	M	Normal	7 0
P W	28	M	Normal	4 0
R. P	26	M	Normal	3 5
D C.	34	M	Normal	6 0
J I	26	M	Normal	6 0
G. F	28	M	Normal	6 5
H. P	33	M	Cirrhosis of the liver	9 0
A. B.	43	M	Colloid goiter	7 0
D E.	29	F	Psoriasis	6 5
W W	26	F	Tonsillectomy	3 5
M Y	14	F	Tonsillectomy	6 5
K. W	51	F	Peptic lcer	6 5
J H	38	M	Thyroidectomy	8 0
D M	22	M	Tonsillectomy	8 0
Mean				6 12
S D				1 8

the relationship between diastolic pressures and the diastolic waves of the apexcardiogram has been expressed as the correlation co-efficient.

Results

For the 21 subjects without evidence of heart disease the mean height of the presystolic wave of the apexcardiogram expressed as a percentage of the total amplitude of deflection was 6 per cent (S D 2 per cent) The presystolic wave was not greater than 9 per cent in any patient (Table I)

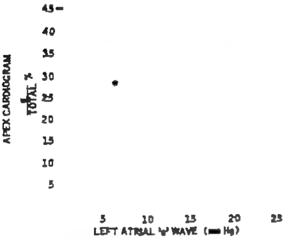

Fig 3 No significant correlation between the presystolic wave of the apexcardiogram and the left atrial systolic pressure wave.

In the group of 20 patients with aortic stenosis a large presystolic wave exceeding 10 per cent of the total deflection was present in 18 (90 per cent of the patients studied) The mean height of the presystolic wave for the group was 21 per cent (S D 10 per cent) and this wave was less than 10 per cent in only two patients. The difference between the mean of 6 per cent for the subjects without heart disease and the mean of 21 per cent for the patients with aortic stenosis is highly significant (t = 16 35 p < 0 01)

The left atrial systolic pressure wave was measured in 19 patients the onset of atrial fibrillation during cardiac catheterization preventing the measurement in the remaining patient The average height for the 19 patients was 11 mm Hg (range 6 to 22 mm Hg)

A third sound point was identified on the apexcardiogram in 16 patients 80 per cent of the patients with aortic stenosis, and the height of this point was measured in each case the mean value for the group being 10 per cent (S D 9 per cent) The average left ventricular end-diastolic pressure for the 20 patients was 12 mm Hg with a range from −5 to 30 mm Hg

Comparison of apexcardiogram with intracardiac pressures In Fig 3 the height of the presystolic wave in the apexcardiogram has been compared with the left atria

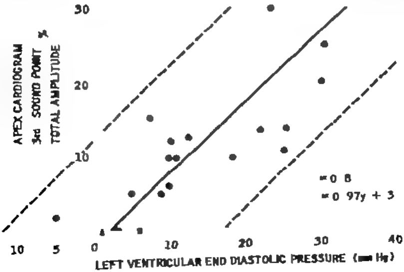

Fig 4 Regression line for best estimate of left ventricular end-diastolic pressure (continuous line) with interrupted lines at two standard errors of estimate.

systolic pressure No significant correlation is demonstrable ($r = 0.39$ $p > 0.05$)

When the height of the third sound point is compared with the left ventricular end diastolic pressure in each patient (Fig 4) a highly significant correlation is found $r = 0.8$ $p < 0.001$ The regression equation for the prediction of left ventricular end diastolic pressure (x) from the height of the third sound point (y) is $x = 0.97y + 3$ In Table II the heights of the third sound points on the apexcardiogram have been used in the regression equation to predict left ventricular end-diastolic pressures, and the predicted values are compared with those measured during catheterization.

Discussion

Precordial vibrations have a frequency range from 0 to 1,500 c.p.s. and only a small proportion of these vibrations are below the audible range. The amplitude of these infrasonic vibrations is large and they have usually been recorded by means of an air tube connected to a crystal pick up.[4] Roberts and Sherwood Jones[7] point out however that the low frequency response of the widely used crystal microphone may introduce serious distortions of the apexcardiogram The instrument used in the present study has a satisfactory frequency response from 0 to 50 c.p.s. and the apexcardiogram obtained is an accurate record of the movements of the apex beat relative to the rib cage.

The presystolic wave of the apexcardiogram The presystolic wave of the apex cardiogram represents active filling of the left ventricle due to left atrial contraction.[8] The presystolic wave is closely related to the P wave of the ECG the onset of the P wave preceding the onset of this wave by 0.11 sec., and in the presence of complete atrioventricular dissociation the presystolic wave continues to follow this close relationship with the P wave Furthermore in the presence of atrial fibrillation the presystolic wave is no longer seen.

From a study of 52 normal subjects, Benchimol and Dimond determined a mean height for the presystolic wave of the apexcardiogram of 7.8 per cent and this is in reasonable agreement with the mean of 6 per cent for subjects without heart disease in the present investigation The presystolic wave of the apexcardiogram has been shown to be abnormally large in aortic stenosis by Braunwald and associates[1] and Goldblatt and co-workers[9] and a significant difference has also been demonstrated here An abnormally large presystolic wave implies greater filling of the left ventricle than normal during atrial systole and may be the result of an increased force of atrial contraction or of an altered distensibility of the ventricle. Both of these factors will be considered

Force of the left atrial systole The average pulse pressure of left atrial systole for normal subjects is 3.4 mm Hg with a range of 1 to 7 mm Hg The a wave in the left atrial pressure pulse is therefore abnormally high in most of the patients with aortic stenosis in the present study but this cannot be the sole factor determining the abnormally large presystolic wave in the apexcardiogram as there is no significant correlation between the pressure wave

Table II Prediction of left ventricular end diastolic pressure (LVEDP) in 20 patients with aortic stenosis

LVEDP (mm. Hg)		Difference
Predicted from apexcardiogram	*Measured at catheterization*	*Measured value-predicted value*
22	30	8
9	10	1
16	25	9
12	10	− 2
3	6	3
5	−5	−10
12	10	− 2
15	1	3
15	10	− 5
32	22	−10
27	30	3
13	25	12
8	5	− 3
16	22	[illegible]
12	[illegible]	6
7	8	1
3	3	0
3	0	− 3
[illegible]	7	−11
3	0	− 3

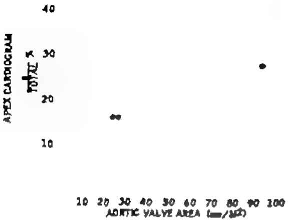

Fig. 5. The height of the presystolic wave of the apexcardiogram is not related to the severity of the aortic stenosis.

and the apexcardiogram presystolic wave in individual patients. Most catheter studies were performed without any premedication and there was no obvious change in the clinical state of the patient between recording the apexcardiogram and obtaining left atrial pressure, so the lack of correlation cannot be ascribed to the interval between the measurements.

Altered distensibility of the left ventricle. Gorlin and associates[13] have shown that the increase in volume of the left ventricle for a given increase in pressure may be abnormally small in aortic stenosis, i.e., the distensibility of the ventricle is reduced. Under these circumstances, filling of the ventricle during early and mid-diastole might be less complete and the contribution of left atrial systole to left ventricular filling augmented, producing a large presystolic filling wave in the apexcardiogram. The lack of correlation between the presystolic wave in the apexcardiogram and the left atrial pressure wave is explained by this hypothesis, for large variations in the distensibility of the left ventricle will occur in individual patients in response to varying degrees of left ventricular hypertrophy and myocardial fibrosis.

It appears that the distensibility of the left ventricle is influenced by factors other than the left ventricular hypertrophy in response to aortic valve stenosis, for when the height of the presystolic wave in the apexcardiogram is compared with the severity of the obstruction to left ventricular outflow no significant correlation is found (Fig. 5). The height of the "a" wave in the apexcardiogram cannot be used to assess the severity of the stenosis.

Third sound point of the apexcardiogram. The rapid filling wave of the apexcardiogram often terminates at a peak which has been termed the third sound point. Dock[13] comments that this peak coincides in timing with the third heart sound and is probably a record of the sharp arrest of the outward motion of the left ventricle when the papillary muscles, chordae tendineae, and mitral valve cusps suddenly limit further expansion of the chamber. When the height of the third sound point is plotted against the left ventricular end-diastolic pressure in the patients with aortic stenosis (Fig. 4) a relationship is apparent. A loud third heart sound in adults is a well accepted sign of heart failure[14] and it might therefore be expected that some correlation would exist between left ventricular end-diastolic pressure, which is usually very high in the presence of left ventricular failure, and the height of the third sound point. From the present findings, it appears that the presence of a high third sound point on the apexcardiogram in adults with aortic stenosis implies a high left ventricular end-diastolic pressure. Possibly the properties of the left ventricle during the early rapid filling phase of diastole are different in children, for a third sound and a third sound point are normally present in young people. The apexcardiogram cannot be expected to give the same indication of the left ventricular diastolic pressure in children as is found in adults with aortic stenosis.

Conclusions

The presystolic thrust of the cardiac apex beat caused by left atrial systole is abnormally large in many patients with aortic stenosis. The size of this presystolic wave does not reflect the severity of the obstruction to left ventricular outflow in the individual case, nor does it correlate well with the magnitude of the left atrial pressure wave. It is believed that the lack of correlation between the size of the presystolic apical impulse and the left atrial

pressure wave indicates variations in compliance of the left ventricle in aortic stenosis.

The height of the third sound point in the apexcardiogram in adults with aortic stenosis correlates well with the left ventricular end-diastolic pressure an elevated end-diastolic pressure and a high third sound point being found together in left ventricular failure.

REFERENCES

1. Nixon, P. G. F., Hepburn, F., and Ikram, H.: Simultaneous recording of heart pulses and sounds, Brit. M. J. 1:1169, 1964.
2. Fleming, J., and Hamer, J.: Effect of propanolol on left atrial systole in ischaemic and hypertensive heart disease, Brit. Heart J. 29:257, 1967.
3. Tafur, E., Cohen, L. S., and Levine, H. D.: The normal apexcardiogram, Circulation 30:381, 1964.
4. Benchimol, A., and Dimond, E. G.: The apex cardiogram in ischaemic heart disease, Brit. Heart J. 24:581, 1962.
5. Rappaport, M. B., and Sprague, H. B.: The graphic registration of the normal heart sounds, Am. Heart J. 23:591, 1942.
6. Luisada, A. A., and Magri, G.: The low frequency tracings of the precordium and epigastrium in normal subjects and cardiac patients, Am. Heart J. 44:545, 1952.
7. Roberts, D. V., and Sherwood Jones, E.: A new system for recording the apex-beat, Lancet 1:1193, 1963.
8. Coulshed, N., and Epstein, E. J.: The apex cardiogram: its normal features explained by those found in heart disease, Brit. Heart J. 25:697, 1963.
9. Braunwald, E., Goldblatt, A., Aygen, M. M., Rockoff, S. D., and Morrow, A. G.: Congenital aortic stenosis, Circulation 27:426, 1963.
10. Goldblatt, A., Aygen, M. M., and Braunwald, E.: Haemodynamic-phonocardiographic correlations of the fourth heart sound in aortic stenosis, Circulation 26:92, 1962.
11. Braunwald, E., Brockenbrough, E. C., Frahm, C. J., and Ross, J., Jr.: Left atrial and left ventricular pressure in subjects without cardiovascular disease, Circulation 24:267, 1961.
12. Gorlin, R., Rolett, E. L., Yurchak, P. M., and Elliott, W. C.: Left ventricular volume in man measured by thermodilution, J. Clin. Invest. 43:1203, 1964.
13. Dock, W.: Heart sounds from Starr-Edwards valves, Circulation 31:801, 1965.
14. Wood, P.: Diseases of the heart and circulation, 2nd ed., London, 1956, Eyre & Spottiswoode, Ltd.

The effect of the β-adrenergic antagonist propranolol on rabbit atrial cells with the use of the ultramicroelectrode technique

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The mechanism by which β-adrenergic antagonists inhibit cardiac arrhythmias has not been fully defined There is increasing clinical evidence that these agents will abolish certain digitalis-induced arrhythmias, that they will decrease ventricular rate in presence of atrial fibrillation or atrial flutter and that they will reduce atrial rate in atrial and nodal tachycardias. This antiarrhythmic property of β-adrenergic blocking drugs has been ascribed to a specific blocking of β-adrenergic receptors and to a quinidine like effect unrelated to β-adrenergic blockade.[3]

Studies of the effect of a β blocking agent, propranolol† were undertaken in isolated perfused atrial tissue, thus excluding neural and humoral factors. The microelectrode technique of recording single cell transmembrane potentials permits precise quantitative analysis of the effects of the drug upon various parameters of the action potential.

Methods

Atria were dissected rapidly from the hearts of stunned New Zealand albino rabbits and standard 1 to 2 cm strips of right atrium without pacemaker tissue were mounted in a plastic perfusion chamber One end of the tissue was fixed to a pair of fine platinum stimulating electrode hooks, while the other end was fixed by fine cotton thread in such a way as to permit isometric contraction The perfusion chamber was mounted in a thermostatically controlled warming bath Nutrient perfusion fluid dripped into the perfusion chamber at a slow constant rate via a warming coil in a water bath and was kept at 36.5° C The perfusion fluid was constantly gassed with 100 per cent oxygen

The tissue was stimulated by a Tektronix pulse generator assembly with interposed isolation transformer A wide range of stimulatory rates were applied but all stimuli were of standard amplitude and duration (10 v 3 msec.)

Transmembrane action potential voltages were obtained from single cells (atrial endocardial surface) by means of glass capillary tube ultramicroelectrodes. Electrode tips were approximately 0 5 μ in diameter The electrodes were filled with

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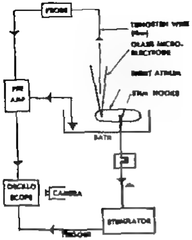

Fig 1 Diagrammatic representation of method of recording transmembrane potential.

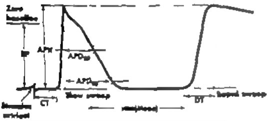

Fig 2 Diagram illustrating the method of measurement of records of action potentials. *RP* resting potential (mv) *CT* conduction time (msec.) *APH* action potential height (mv) APD_{50} and APD_{90}, action potential durations at 50 per cent and 90 per cent of repolarization (msec) *DT* depolarization time (msec)

a 3M solution of potassium chloride by boiling in negative-pressure atmosphere and were subsequently mounted on fine tungsten wire. Negative capacitance probes were utilized (Medistor) and following suitable amplification transmembrane potentials were displayed on a Tektronix dual-beam oscilloscope and photographically recorded Amplification was such that a 20 mv signal resulted in a 1 cm vertical deflection of the oscilloscope beam (Fig 1)

The rabbit atria were perfused with a modified Ringer s solution of the following composition in mmole per liter NaCl 154 NaH_2Co 5 9 dextrose 5 0 $CaCl_2$, 2 2; KCl 2 7 Propranolol was used in a concentration of 1 mg per liter of modified Ringer s solution.

The experimental procedure was as follows

A. The atrium was perfused with the modified Ringer s solution for one hour Subsequently transmembrane potentials were recorded photographically at the following stimulatory rates 60 95 120 150 188 and 240 stimuli per minute and at the maximum follow rate. Propranolol in a concentration of 1 mg per liter of modified Ringer s solution was then perfused through the tissue bath for one hour following which transmembrane action potentials were again recorded at the same stimulatory rates (15 experiments)

B Conduction velocity was measured in one experiment by simultaneous impalement of two atrial cells a measured distance apart Conduction velocity was determined at a stimulatory rate of 95 beats per minute before and after addition of propranolol to the perfusing fluid

C Self-sustaining atrial arrhythmias were produced in the atrial tissue by perfusing the atrium with Ringer s solution containing acetylcholine (300 γ per liter) and applying bursts of rapid stimuli (interstimulatory interval 6.3 msec.) Similar experiments were performed following addition of propranolol (1 mg per liter) to the Ringer s solution containing acetylcholine (300 γ per liter)

D The spontaneous contraction rate of a segment of atrial tissue including the sinoatrial node, was determined before and approximately one hour after addition of propranolol to the perfusion fluid In all instances, a negative chronotropic effect was observed

E. In five separate experiments the positive chronotropic effect of isoproterenol (400 γ per liter) on the spontaneous contraction rate was confirmed Addition of isoproterenol in similar concentration to the perfusion fluid following exposure of the tissue to propranolol for one hour (1 mg per liter) did not result in any increase in spontaneous contraction rate.

Action potential parameters were measured directly from the photographic records in order to quantitate changes (Fig 2) The resting potential (*RP*) was measured in millivolts from the zero baseline verti-

Table I. The effects on rabbit atria of addition of propranolol (1 mg./L.) to the modified Ringer's solution

	Control		Propranolol	
	Mean value	No. of observations	Mean value	No. of observations
Spontaneous rate (beats/min.)	155 ± 19.5	15	117 ± 17.5	14
Maximum follow rate (beats/min.)	630 ± 125	14	235 ± 67	14
Refractory period (msec.)	67 ± 16.5	13	114 ± 48	10*
Stimulation threshold (v.)	0.82 ± 0.53	15	1.46 ± 1.0	13

*p < 0.01

cally to a point just preceding depolarization. At most stimulatory rates, measurements were recorded only if the RP was greater than 65 mv. The action potential height (*APH*) was measured in millivolts as a maximum vertical height of depolarization. Conduction time (*CT*) in msec. was measured from the start of the stimulus artifact to the onset of depolarization. Repolarization was quantitated by measuring its duration in milliseconds at the 50 per cent and 90 per cent levels of repolarization (APD_{50}, APD_{90}). Depolarization time (*DT*) was measured in milliseconds from its onset to completion.

Maximum follow rates (*MFR*) expressed as beats per second were determined in all experiments as a convenient index of effective refractory period. Direct measurements of refractory period were obtained by applying paired pulses to the tissue. Primary driving stimuli occurred at 630 msec. intervals. A second testing pulse was applied at diminishing intervals after the primary pulse until an action potential could not be evoked utilizing maximum voltage.

The tissue excitation threshold was determined in all experiments before and following addition of propranolol to the perfusing fluid. The threshold voltage was recorded directly from the calibrated scale of the Tektronix stimulation unit.

The results of 17 experiments are reported and are expressed as mean values ± one standard deviation. The number of observations comprising that mean follow in brackets. The t test was applied to the difference of all paired data. Differences of means having probability values (P) less than 0.05 were considered significant. The data were transferred to IBM punch cards. Means, standard deviations, and T values were calculated by an IBM 7040 digital computer.

Results

Following addition of propranolol to the perfusion fluid, the spontaneous contraction rate of a segment of atrium including the sinoatrial node slowed in all instances (Table I).

Addition of isoproterenol to the perfusion fluid invariably resulted in a prompt acceleration in spontaneous contraction rate, whereas addition of isoproterenol in the presence of propranolol did not result in any change in the contraction rate.

With increasing frequency of stimulation, the transmembrane action potentials of atrial cells display predictable changes as illustrated in panels *A*, *C*, and *E* of Fig. 3. Following addition of propranolol to the perfusing fluid further marked changes in the characteristics of the action potential occur (panels *B*, *D*, and *F*, Fig. 3).

Conduction time in the control series increased at rapid stimulatory rates. Addition of propranolol resulted in a significant prolongation of conduction time at all stimulatory rates and profound retardation at the maximum follow rate (Table II, Fig. 4). Conduction velocity was determined in one experiment and was found to decrease from 0.5 to 0.3 M per second following addition of pro-

Table II. The effects on atrial transmembrane potentials of addition of propranolol to modified Ringer's solution

Stimulatory rate (beats/min.)	Period	Conduction time (msec.) Mean value	No. of observations	Depolarization time (msec.) Mean value	No. of observations	Repolarization time (msec.) APD_{50} Mean value	No. of observations	APD_{90} Mean value	No. of observations	Resting potential (−mv.) Mean value	No. of observations	Action potential height (mv.) Mean value	No. of observations
60	S	13 ± 4.5	15	2.8 ± 0.5	14	30 ± 5.2	11	66 ± 4.9	10	73 ± 3.8	11	86 ± 6	11
	P	20 ± 6.5	15*	4.4 ± 1.3	13*	28 ± 6.6	[illegible]	65 ± 6.6	10	69 ± 4.4	11	72 ± 7	11
95	[illegible]	13 ± 5.1	15	2.8 ± 0.7	13	31 ± 5.5	11	85 ± 11.1	11	71 ± 4.3	11	81 ± 12	11
	P	23 ± 7.9	15*	5.5 ± 1.7	13*	33 ± 4.5	11	88 ± 14.2	10	70 ± 4.4	9	78 ± 6	10*
120	S	12 ± 4.0	18	2.9 ± 0.7	14	30 ± 7.0	13	83 ± 12.0	13	71 ± 4.7	13	79 ± 10	13
	P	26 ± 9.5	15	5.6 ± 1.4	13*	33 ± 4.5	11	96 ± 9.3	9	70 ± 3.1	8	74 ± 4.7	8*
150	S	13 ± 4.2	15	3.1 ± 0.5	15	31 ± 7.1	12	85 ± 13.5	11	73 ± 4.6	11	83 ± 12.2	11
	P	29 ± 13.3	14	6.0 ± 1.3	11	32 ± 4.9	8	93 ± 10.3	6	71 ± 3.1	6	78 ± 3.3	6
155	S	13 ± 4.6	13	3.3 ± 0.8	11	32 ± 7.3	10	83 ± 6.7	8	73 ± 4.2	9	81 ± 11.2	9
	P	31 ± 13.6	9*	7.3 ± 1.5	9*	29 ± 3.3	5	74 ± 10.0	3	69 ± 3.0	4	77 ± 6.1	8
240	S	15 ± 6.6	16	3.0 ± 0.9	14	30 ± 8.3	[illegible]	85 ± 11.2	10	70 ± 3.6	12	78 ± 8.6	12
225 (MFR)	P	44 ± 19.5	16*	10.0 ± 2.8	13*	34 ± 9.5	4	95 ± 31.1	2	65 ± 5.6	4	69 ± 7.9	5
400 (MFR)	S	35 ± 8.0	13	8.7 ± 1.7	13	28 ± 8.0	7	74 ± 7.9	4	65 ± 7.5	5	65 ± 7.0	5

*$p < 0.05$.
S, Modified Ringer's solution; P, propranolol 1 mg. per liter; MFR, maximum follow rate; APD_{50}, action potential duration at 50 per cent level of repolarization; APD_{90}, action potential duration at 90 per cent level of repolarization.

pranolol (stimulatory rate 95 beats per minute).

With increasing stimulatory rates depolarization time was prolonged significantly by propranolol to much greater degree than as observed under control conditions (Table II, Fig. 5).

Although the stimulatory threshold was increased in all experiments following addition of propranolol to the perfusion fluid (Table I), a significant change in RP was not observed (Table II). Perhaps with exposure of the tissue to higher concentrations of propranolol alteration of RP would have occurred. Clearly, however, the excitability and conduction characteristics of atrial cells are altered by propranolol, these effects being most pronounced at rapid stimulatory rates.

The duration of repolarization (APD_{50} and APD_{90}, Table II) was slightly increased by addition of propranolol although these changes are not statistically significant. Nevertheless, propranolol does result in a marked and significant reduction in maximum follow rate and a prolongation of absolute refractory period (Table I), indicating that alteration in the repolari-

zation and postexcitation recovery processes have occurred.

Following addition of acetylcholine to the perfusion solution brief bursts of rapid stimuli readily induced rapid self-sustaining arrhythmias with single cell discharge rates averaging 750 beats per minute. After exposure of the tissue to propranolol these acetylcholine potentiated arrhythmias could not be induced.

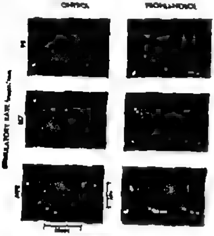

Fig. 3. Sequence of action potentials from rabbit atrial cells showing control and propranolol effects at three stimulatory rates.

Time calibration panels A to E, slow sweep = 80 msec., rapid sweep = 20 msec. Time calibration panel F: slow sweep = 200 msec., rapid sweep = 40 msec. Voltage calibration = 80 mv. Panels A, C, and E, Control, Ringer solution, MFR = 880 beats per minute. Panels B, D, and F, Propranolol 1 mg. per liter of Ringer solution, MFR = 284 beats per minute.

Discussion

Propranolol has a profound effect on the transmembrane potentials of rabbit atrial cells in vitro. In the concentration of propranolol used in these experiments the effects are most striking at rapid stimulatory rates and include a prolongation of conduction time, a reduction in rate of depolarization, and a prolongation of effective refractory period. Action potential amplitude was reduced by propranolol but the RP was not altered; the reduction in action potential amplitude accordingly is due to a diminution of positive overshoot. Hoffman and Singer[8] also observed that propranolol in a concentration of 1 mg. per liter usually did not alter resting potential significantly in canine His-Purkinje fibers although higher concentrations resulted in reduction of RP. Threshold voltages were increased by addition of propranolol. These effects closely parallel those of quinidine on atrial cell action potentials.[6]

The frequency dependency of the effects of propranolol on conduction time and depolarization time is very evident. Although prolongation of repolarization by propranolol in this concentration was not prominent, effective refractory period was prolonged significantly. This implies that the postexcitation recovery process is retarded by propranolol. West and Amory[7] in their analysis of quinidine effect on atrial cells suggested a similar alteration of the recovery process.

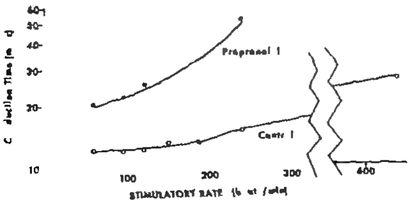

Fig. 4. Conduction time plotted relative to stimulatory rate for atrial tissue in modified Ringer solution and following addition of propranolol 1 mg. per liter.

Propranolol in each experiment resulted in a significant reduction in spontaneous pacemaker discharge rate. There are two possible explanations for this reduction (1) there may be a direct action of the drug on the pacemaker cells with alteration in the depolarization and repolarization process as has been demonstrated with quinidine or (2) there may be a pharmacologic blockade of β-adrenergic effects of catecholamines within the pacemaker tissue. Propranolol in the concentration used had a β blocking function as was confirmed by its blockade of isoproterenol chronotropic effects. In view of the similarity of effect of quinidine and propranolol on atrial cells, and because quinidine has a demonstrated direct effect on the pacemaker action potential it seems most likely that reduction in spontaneous pacemaker discharge rate is a direct effect of propranolol.

Sekiya and Vaughan Williams have demonstrated that another β blocking agent Pronethalol has similar effects on conduction time and repolarization. The dextro isomer of Pronethalol which has only 2 5 per cent of the β-adrenergic blocking activity of DL Pronethalol is as effective in abolishing ouabain induced arrhythmias as is DL Pronethalol. This again suggests that these drugs may act as β-adrenergic blockers and also as primary antiarrhythmic agents functioning at the cellular level.

The mechanism whereby propranolol alters membrane potential characteristics is yet to be defined The transmembrane potential is primarily dependent upon the relative intra and extracellular concentrations of sodium and potassium ions. RP and the process of repolarization are chiefly dependent upon potassium ion concentrations, whereas the depolarization process is mainly dependent upon sodium ion concentrations As previously noted the effects of propranolol closely parallel those of quinidine on the transmembrane action potential with marked retardation of depolarization process at rapid stimulatory rates. The effect of quinidine on depolarization can be reversed by increasing the extracellular fluid sodium ion concentration.[14] Possibly propranolol may act by inhibition of the exchange of sodium and potassium across the cell membrane

A burst of rapid stimuli will induce in isolated atrial tissue a rapid self-sustaining arrhythmia. Exposure of the tissue to propranolol prior to addition of acetylcholine blocks completely the occurrence of these self-sustaining arrhythmias. This pronounced antiarrhythmic activity of propranolol may be due to a combination of reduced cellular excitability with suppression of spontaneous depolarization

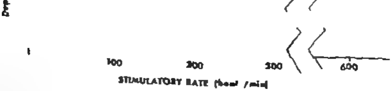

Fig 3 Depolarization time plotted relative to stimulatory rate for atrial tissue in modified Ringer's solution and following addition of propranolol 1 mg per liter

and decreased conduction velocity. Acetylcholine increases repolarization rate;[11] possibly propranolol inhibits potassium conductance so blocking this effect of acetylcholine.

Major changes in intracellular potassium concentration would be reflected in diminished RP but such a change was not seen in these experiments following exposure of the tissue to propranolol. Rather the electrophysiological changes observed are likely more closely related to alterations in sodium ion concentrations and flux, paralleling the effect of quinidine. This conclusion is in agreement with that of Vaughan Williams[12] who studied the effect of propranolol on rabbit atrial muscle.

Summary

The effect of the β-adrenergic blocking agent propranolol was studied by the ultramicroelectrode technique of recording transmembrane action potentials. The atria of stunned albino rabbits were perfused in vitro with a modified Ringer's solution. Transmembrane action potentials were recorded from single cells at a variety of stimulatory rates before and following addition of propranolol in a concentration of 1 mg. per liter. A quinidine-like effect on transmembrane atrial action potentials occurred with significant retardation of depolarization rate and conduction time and prolongation of effective refractory period. These changes displayed a distinct frequency dependency being most pronounced at rapid stimulatory rates.

The negative chronotropic effect of propranolol on the spontaneous discharge rate of the sinoatrial pacemaker was observed and the ability of propranolol to block the positive chronotropic effect of isoproterenol was confirmed. Propranolol completely inhibited induction of acetylcholine potentiated arrhythmias. The data strongly supports the concept that the antiarrhythmic properties of propranolol may be due to a direct effect on atrial cells independent of a β-adrenergic blocking activity.

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REFERENCES

1. Vaughan Williams, E. M., and Sekiya, A.: Prevention of arrhythmias due to cardiac glycosides by block of sympathetic β-receptors, Lancet 1:420, 1963.
2. Stock, J., and Dale, N.: Beta-adrenergic blockade in cardiac arrhythmias, Brit. M. J. 2:1230, 1963.
3. Harrison, D., Griffin, J. R., and Fiene, T.: Effects of beta-adrenergic blockade with propranolol in patients with atrial arrhythmias, New England J. Med. 273 (8): 410, 1965.
4. Dawes, G. S.: Synthetic substitutes for quinidine, Brit. J. Pharmacol. 1:90, 1946.
5. Hoffman, B. F., and Singer, D. H.: Appraisal of the effects of catecholamines on cardiac electrical activity, Ann. New York Acad. Sc. 139:914, 1967.
6. Vaughan Williams, E. M.: The mode of action of quinidine on isolated rabbit atria interpreted from intracellular potential records, Brit. J. Pharmacol. 13:276, 1958.
7. West, T. C., and Amory, D. W.: Single fiber recording of the effects of quinidine at atrial and pacemaker sites in the isolated right atrium of the rabbit, J. Pharmacol. & Exper. Therap. 130 (2):183, 1960.
8. Sekiya, A., and Vaughan Williams, E. M.: A comparison of the anti-fibrillatory actions and effects on intracellular cardiac potentials of Pronethalol, disopyramide, and quinidine, Brit. J. Pharmacol. 21:473, 1963.
9. Lucchesi, B. R.: The effects of Pronethalol and its dextro isomer upon experimental cardiac arrhythmias, J. Pharmacol. & Exper. Therap. 148 (1):94, 1965.
10. Cox, A. R., and West, T. C.: Sodium lactate reversal of quinidine effect studied in rabbit atria by the micro-electrode technique, J. Pharmacol. & Exper. Therap. 131(2):212, 1961.
11. Hoffman, B. F., and Cranefield, P. F.: Electrophysiology of the heart, New York, 1960, McGraw-Hill Book Company, Inc.
12. Vaughan Williams, E. M.: Mode of action of beta receptor antagonists on cardiac muscle, Am. J. Cardiol. 18:399, 1966.

The effect of digitalization on quinidine toxicity

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Studies are not conclusive concerning additive toxicity of digitalis and quinidine. Gold and associates[1] showed that large doses of quinidine given to dogs with digitalis-induced ventricular tachycardia often caused asystole. Mosey and Tyler[2] found that ouabain-induced ventricular tachycardia was abolished by 5 to 20 mg. per kilogram doses of quinidine.

Kwit and Gold[3] found that small doses of quinidine, 2 mg. per kilogram, given to less severely digitalis-intoxicated dogs often caused a decrease in first-degree atrioventricular (AV) block, but that 17 to 35 mg. per kilogram doses often initiated ventricular tachycardia in the same dogs. Dogs not given digitalis did not develop ventricular tachycardia with quinidine dosage of 40 mg. per kilogram.

Rodensky and associates studied the tolerance of dogs to digoxin after cardiographic evidence of quinidine effect was produced by an infusion of quinidine. The lethal dose of digoxin was decreased for some animals but was not statistically significantly reduced. Lucchesi and co-workers,[5] found contrary results.

In man, Acierno and Gubner[6] treating 44 patients with intravenous quinidine concluded that there was "no evidence that previous digitalization enhanced the therapeutic effect," but state that "quinidine is hazardous in arrhythmias due to digitalis toxicity."

In man, it is common practice to use quinidine in fully digitalized patients, but it is difficult to obtain data on quinidine tolerance in humans. Although there are many investigations of the effect of quinidine on digitalis intoxication[1-6] there are few data on the effect of digitalis on quinidine intoxication. In this study digitalized but not digitalis-toxic dogs were investigated to find if there are differences in quinidine tolerance between those given digitalis and those not. Serum potassium and quinidine levels at various stages of quinidine intoxication were also measured to help elucidate mechanism of drug action.

Methods

A total of 20 mongrel dogs (10 to 20 kilograms) were anesthetized with pentobarbital sodium (20 mg. per kilogram intravenously) and a tracheotomy tube was inserted. The femoral artery and vein were cannulated with polyethylene catheters. One hundred per cent oxygen was administered by employing a demand valve in the first six dogs and by intermittent positive

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pressure in the remaining 14 dogs. Ten dogs received a digitalizing dose of desacetyl-lanatoside C hereafter referred to as Cedilanid D (0 0258 mg per kilogram) equivalent to a full human digitalizing dose. After 20 minutes had elapsed quinidine gluconate 1 mg per kilogram per minute diluted in normal saline, was infused intravenously Ten other dogs received only the quinidine infusion One dog from each group was studied in alternate sequence Prior to the infusion and at 30 minute intervals during the quinidine infusion arterial samples of blood were drawn in heparinized syringes for the determination of quinidine and potassium and mean aortic blood pressure and electrocardiogram (ECG) recorded Serum quinidine was analyzed in duplicate by the method of Brodie and Udenfriend and duplicate serum potassium measured with an internal standard Baird flame photometer A Sanborn model 150 recorder with a Statham P23Db strain gauge was used to record mean aortic blood pressure. QRS duration was measured from tracings recorded at 50 mm per second

Results

1 Prior to quinidine infusion the mean aortic blood pressure was similar in both the digitalized dogs and those not digitalized The slower heart rate in the digitalized dogs was not statistically significantly different from the other group (Table I) The QRS duration and serum potassium were similar in both groups prior to quinidine infusion

2 Quinidine toxicity The duration of quinidine infusion and therefore total quinidine dose QRS duration, serum potassium and quinidine levels at the

Table I Mean values prior to quinidine infusion

	N Cedilanid-D (10 dogs)	*Cedilanid D (10 dogs)*	*Probability*
Serum K+ (mEq./L.)	3 5 (S.D 0 42)	3 7 (S.D 0 32)	0 6 > p > 0 5
QRS duration (sec.)	0 037 (S.D 0 010)	0 041 (S.D 0 011)	0 5 > p > 0 4
Rat (beats/min.)	155 6 (S.D 44 2)	137 9 (S.D 35 8)	0 1 > p > 0 05
Mean B.P	120	121	

*S D = Standard deviation.

Table II Mean values at death

	Quinidine gluconate only (10 dogs)	*Cedilanid-D and quinidine gluconate (10 dogs)*	*Probability*
Duration of infusion (min.)	144 5 (S.D 38 6)	151 5 (S.D 36 6)	0 7 > p > 0 6
Serum quinidine (mg /L.)	59 4 (S.D 13 1)	54 7 (S.D 13 1)	0 5 > p > 0 4
QRS duration† (sec.)	0 087 (S.D 0 019)	0 077 (S.D 0 035)	0 5 > p > 0 4
Serum K+ (mEq./L.)	3 8 (S.D 0 72)	4 1 (S.D 0 77)	0 4 > p > 0 3

After beginning of quinidine infusion.
†Taken less than ½ hour before death.

time of death were similar in both the digitalized dogs and those not digitalized (Table II). Six digitalized and two dogs not digitalized died from arrhythmias before lengthening of QRS to twice its original duration ($0.2 > p > 0.1$).

Discussion

These results indicate that there is no difference between animals digitalized and not digitalized in respect to quinidine toxicity. The amount of quinidine infused, the quinidine levels, and the serum potassium levels at death are similar in both groups. This experiment shows no adverse or significant beneficial effects of prior digitalization.

There was no evidence of digitalis intoxication as indicated by premature beats. A full digitalizing dose of a rapidly acting digitalis preparation was used. The mean duration of quinidine infusion was between two and three hours, a period during which digitalis effect should have been considerable.

There is a suggestion that prior digitalization had an effect on quinidine-induced QRS prolongation. That is, 6 of 10 digitalized dogs developed quinidine-induced arrhythmias before marked QRS prolongation was observed. This occurred in only 2 of 10 dogs without prior digitalization. This is not a statistically significant difference.

This study supports the clinical impression that there is no excessive risk in the use of quinidine during digitalis administration.

Summary

The effect of quinidine on digitalized but not digitalis-intoxicated dogs was studied. One group was digitalized with a full-digitalizing dose of Cedilanid D prior to an infusion of quinidine gluconate. Another group was given quinidine without prior digitalization. The mean blood pressure, heart rate, QRS duration, and serum potassium levels after Cedilanid D but prior to quinidine infusion were not significantly different for the two groups. Six digitalized dogs and two undigitalized animals died before lengthening of the QRS duration to twice control values. This was not a statistically significant difference. The time of death and thus the amount of quinidine infused, the serum potassium and quinidine levels at death were not statistically different in the two groups. It was concluded that prior digitalization with a rapid-acting digitalis preparation has no significant effect on quinidine toxicity.

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REFERENCES

1. Gold, H., Modell, W., and Price, L. Combined actions of quinidine and digitalis on the heart, Arch. Int. Med. 50:766, 1932.
2. Mosey, L., and Tyler, M. D. The effect of diphenylhydantoin sodium (Dilantin), procaine hydrochloride, procaine amide hydrochloride, and quinidine hydrochloride upon ouabain-induced ventricular tachycardia in unanesthetized dogs, Circulation 10:65, 1954.
3. Kwit, N. T., and Gold, H. Further experimental observations on the combined effects of digitalis and quinidine on the heart, J. Pharmacol. & Exper. Therap. 50:160, 1934.
4. Rodensky, P. L., Rathe, J. H., and Wasserman, F. The effect of quinidine on tolerance to digitoxin, Am. J. Cardiol. 5:498, 1960.
5. Loeb, B. R., and Shivak, R. Effect of quinidine and procainamide upon acetylstrophanthidin cardiotoxicity, J. Pharmacol. & Exper. Therap. 143:366, 1964.
6. Acierno, L. J., and Gubner, R. Utility and limitations of intravenous quinidine on arrhythmias, Am. Heart J. 41:733, 1951.
7. Brodie, B. B., and Udenfriend, S. The estimation of quinidine in human plasma, with a note on the estimation of quinidine, J. Pharmacol. & Exper. Therap. 78:154, 1943.

Case reports

Diastolic murmurs due to two sequelae of atherosclerotic coronary artery disease: Ventricular aneurysm and coronary artery stenosis

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Diastolic murmurs due to atherosclerotic involvement of the coronary arteries, the major type of cardiac abnormality in this country, are rarely encountered. The following two case reports illustrate two unusual causes of diastolic murmurs, both arising from common complications of atherosclerotic coronary artery disease.

Ventricular aneurysm

Ventricular aneurysm following myocardial infarction is a frequent event. This complication has been found in 15 per cent of patients with a history of myocardial infarction.[1-4] The lack of usefulness of cardiac murmurs in establishing the antemortem diagnosis has been noted in several reviews of the subject.[1,2,4] A short systolic and a long diastolic murmur have, however, been described by Scherf and Brooks[5] in three cases of ventricular aneurysm. These authors suggested that the murmurs were probably due to the passage of blood into the ventricular aneurysm during systole and back into the left ventricle during diastole. Origin of the diastolic murmur at the aortic valve was considered unlikely due to the absence of other signs of aortic regurgitation. The following case report demonstrates that in the absence of any intrinsic disease of the aortic valve leaflets, aortic regurgitation of major degree occurred as a complication of myocardial infarction and ventricular aneurysm formation. The onset of aortic regurgitation following documented myocardial infarction may, therefore, serve as a clue to the diagnosis of ventricular aneurysm.

Case report

Case 1. J. W., a 53-year-old man, sustained an anterolateral myocardial infarction in June, 1964, at which time no cardiac murmurs were heard. Upon his discharge from the hospital six weeks later both systolic and diastolic murmurs were noted. Chest films revealed increasing heart size and pulmonary congestive changes. In December, 1964, because of dyspnea and orthopnea, he was treated with digitalis and diuretics. He entered his

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local hospital again on February 16, 1965 because of intractable heart failure and was transferred to Yale–New Haven Medical Center on February 23 1965 for consideration of aortic valve replacement. Physical examination revealed a dyspneic acutely ill, middle-aged man. Blood pressure was 110/50 pulse was 96 and regular and respirations were 24 per minute. There were bilateral moist râles at the lung bases. Arterial pulses were brisk throughout. The jugular venous pulse was markedly accentuated. There was a diffuse left ventricular heave without paradoxic pulsation. A protodiastolic filling gallop, a grade 2/6 ejection murmur and grade 4/6 left sternal border decrescendo blow were present. The liver was enlarged 10 cm. below the right costal margin, but there was no edema. Laboratory studies revealed a hematocrit of 40 per cent with normal white blood cell count and differential. Urine analysis was normal. Blood urea nitrogen was 43 mg per cent. Serum electrolytes were normal. A chest film revealed marked cardiomegaly with bilateral pleural effusions. An electrocardiogram (ECG) revealed Q waves in I AVL, and V_1-V_6. RS-T elevations were noted in V_1-V_6 (Fig 1). Because of the recent onset of an aortic diastolic murmur the diagnosis of rupture of a sinus of Valsalva was considered. Accordingly on February 24, 1965 angiograms to demonstrate the left ventricle and aorta were performed. These films revealed a markedly thinned left ventricular wall and also demonstrated aortic valve regurgitation (Fig 2). The ascending aorta was normal. The right atrial mean pressure was 16 mm. Hg Left ventricular pressure was 106/40 and central aortic pressure was 106/36. Based on the catheterization and angiographic findings of aortic regurgitation and a left ventricular aneurysm, plans were initiated to replace the aortic valve and perhaps resect the ventricular aneurysm. On the following day however the patient suffered cardiac arrest and, although initial resuscitation was successful, he died three hours later

At postmortem examination, the pericardial space was almost totally obliterated by fibrous adhesions, being most dense over the anterior surface. The heart weighed 625 grams and showed dilatation of both atria and ventricles. The tricuspid, pulmonic, and mitral valves were normal in appearance. The right ventricular wall measured 5 mm. in thickness near the tricuspid ring and exhibited prominent trabeculae carneae. A large ovoid aneurysm (see the black arrows in Fig 3) measuring 11.0 cm. in length and 5.5 cm. in width was present in the anterior left ventricular wall, extending from the apex to within 5.5 mm. of the aortic ring The aortic subvalvular myocardium averaged 11 mm in thickness. The long axis of the aneurysm was parallel to the left ventricular out

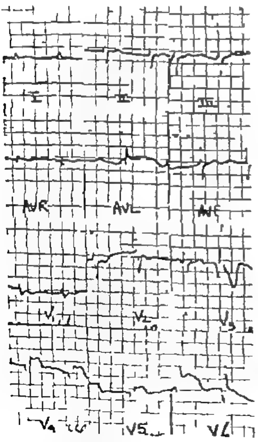

Fig. 1 The ECG of J. W (Case 1) shows Q waves in V_{1-6} of an anterolateral myocardial infarction. Persistent ST-segment elevations in the same leads six months after the acute infarction suggest ventricular aneurysm.

Fig 2 A supravalvular aortic root angiogram in Case 1 demonstrated opacification of the left ventricle with regurgitant jet below the aortic valve (arrows).

Fig 3 Postmortem examination of the heart in Case 1 Note the large anterior wall aneurysm (black arrows) on the right The smaller septal portion is on the left. Note the normal aortic valve and the subvalvular endocardial thickening (white arrows), due to the regurgitant jet.

flow tract and its wall varied between 1 and 3 mm. in thickness. The distal anterior interventricular septum formed the medial portion of the aneurysmal wall. Histologically the wall of the aneurysm was composed of dense collagenous tissue which surrounded occasional atrophic myocardial fibers. Abundant subendocardial elastic fibrils were demonstrated by special stains Several small organizing mural thrombi were attached to the endocardial surface. The papillary muscles were normal. The aortic valve measured 8 0 cm. in circumference and was composed of three slightly opacified but supple cusps whose free margins could be easily approximated in situ The commissures were normal but endocardial pockets were present in the aortic subvalvular region probably indicating antemortem regurgitation (see the white arrows in Fig 3). Gross and microscopic examination of the aortic root was normal. Both coronary arteries were severely involved by atherosclerosis with an old complete occlusion in the left anterior descending branch at the superior apex of the aneurysm. The lungs were congested and edematous the right weighed 1,260 grams and the left 970 grams Microscopic evidence of acute and chronic passive congestion was present. Severe generalized visceral congestion was present especially in the liver The spleen weighed 195 grams and revealed a wedge-shaped zone of coagulative necrosis that measured 1.5 cm. in width at its capsular base. Early peripheral organization of the necrotic zone was present. An adjacent artery contained a partially recanalized thromboembolus.

Discussion

The clinical manifestations of ventricular aneurysm following myocardial infarction vary with the size and anatomy of the lesion. A small aneurysm may be evident only on direct observation as a *local* paradoxic pulsation which causes no identifiable physical signs or symptoms. A large saccular aneurysm arising from a localized region of transmural infarction may be expected to create an abnormal pulsation in the precordial area *medial to the apex* impulse itself [4,7,8] and should be evident by x ray and fluoroscopy as a localized pulsating bulge of the cardiac border provided the contractile vigor of the remaining viable ventricular muscle is maintained Pulsations may be minimal or absent in such aneurysms when they are filled with laminated clot. In the present case, dyskinesis[9] or paradoxic pulsation was not evident, though there was no evidence of large clot by angiographic or postmortem examination The aneurysm was akinetic involving a large area of noncontracting myocardium and causing gross dilatation of the chamber The absence of detectable paradoxic pulsation may be explained not only by reduction of the stroke volume but also by the effect of chamber size on wall movement required for a given stroke volume. In a massively dilated ventricle, only a small radial move

ment of the wall is needed to eject a stroke volume which in a small ventricle would require more pronounced radial movement. In addition, myocardial fibrosis, thickened overlying pericardium and endocardial thickening may prevent expansion of the aneurysm.[10]

The electrocardiographic abnormalities of the present case, consisting of Q waves in Leads I AVL, and V_4-V_6 with persistently elevated RS-T segments in V_4-V_6, were also consistent with the large area of transmural infarction characteristic of an extensive ventricular aneurysm.[11]

The most striking feature of the physical examination in the present case was a diastolic murmur along the left sternal border which appeared sometime after the patient's acute myocardial infarction. This murmur was shown by angiography to be due to regurgitation through an aortic valve which was anatomically intact at postmortem examination. The mechanism of such valvular regurgitation can only be surmised. The aneurysm in the present case did not involve the aortic annulus directly as in the cases of congenital subvalvular left ventricular aneurysms reported by Abrahams and associates.[12] However enlargement of the aortic ring due to left ventricular dilatation and loss of the muscular skeleton of the ventricle surrounding the aortic valve annulus were likely causes of valve incompetence. Scherf and Brooks described diastolic murmurs in three patients with ventricular aneurysms. These authors suggested that the murmurs were due to movement of blood within the aneurysms, and rejected the possibility of aortic regurgitation because of the absence of other characteristic peripheral signs. The bounding pulses and low diastolic blood pressure of aortic regurgitation are due in part however to arteriolar dilatation[13] and may be reduced or absent when congestive failure supervenes.[1] The restoration of arterial diastolic pressure under these conditions is related to the peripheral vasoconstriction characteristic of the failing left ventricle.[13,1] In the present case peripheral signs of aortic regurgitation were minimal and the diastolic blood pressure (50 mm. Hg) was only slightly lower than normal. An aortic root injection nevertheless demonstrated major aortic regurgitation. Therefore, the possibility of aortic regurgitation in the cases of Scherf cannot be excluded.

Recognition that aortic regurgitation may be a consequence of ventricular aneurysm is particularly important because of the possibility of corrective surgery.[17,18] The appearance of a diastolic murmur along the left sternal border in a case where ventricular aneurysm is suspected should raise the suspicion that the genesis of the murmur is aortic insufficiency and not the flow of blood from the aneurysmal sac. Since aortic regurgitation places an added hemodynamic burden upon a ventricle which is already compromised by the aneurysm the prognosis of these patients is extremely poor and surgical correction of the ventricular aneurysm or the valve regurgitation merits consideration.

Coronary artery stenosis

Stenosis in one or more of the coronary arteries is a common postmortem finding but a murmur due to blood flow through a stenosed coronary artery has only recently been reported by Dock and Zoneraich. The following case report describes the appearance of a diastolic murmur in a hypertensive patient in whom there was antemortem evidence of stenosis of the left coronary artery. Certain features of the murmur at auscultation suggested it did not arise from a cardiac valve or from the chest wall. Supravalvular aortography demonstrated an entirely competent aortic valve. The origin of the murmur was therefore felt to be the stenosed left coronary artery. Subsequent marked diminution of the murmur at the time of infarction of that portion of the myocardium normally supplied by this vessel further supported this interpretation.

Case 2. A 55-year-old Caucasian male machinist was referred to the Yale–New Haven Medical Center in January 1962 by his plant physician who, during a routine physical examination, detected a heart murmur that had not been present four months previously. The patient had been seen intermittently on many occasions between 1955 and 1960 at this hospital for treatment of a bleeding duodenal ulcer eventually requiring subtotal gastrectomy and for recurrent cystitis. On no occasion was a cardiac murmur noted. In May 1959 chest x-ray was normal. In 1960 a blood pressure was recorded at 170/116, whereas all previous recordings had been normotensive.

Fig 4 January 1962, PA chest film of the patient in Case 2 shows calcification in the region of the left coronary artery (arrows) and left ventricular hypertrophy

Fig 5 March 1964 retrograde aortogram in Case 2 shows no evidence of aortic insufficiency or aortic root dilatation. There is narrowing of the left anterior descending coronary artery in the region of the calcification noted in Fig 4

On admission to the hospital in January 1962, the patient was asymptomatic. The blood pressure was 180/106 pulse 88, temperature 100° F There were questionable petechiae. The fundi were normal. There was no evidence of congestive heart failure. A grade 2/6 ejection-type systolic murmur at the apex was less audible at the base, and there was a grade 3/6 cooing diastolic murmur at the apex.

Hematocrit was initially 35 per cent, and later rose to 45 per cent. Total and differential white blood cell counts and urine analysis were normal. ECG showed the high voltage and ST T wave changes of left ventricular hypertrophy The left ventricle was prominent in an x-ray film of the chest and *calcification in the region of the proximal* left coronary artery was evident (Fig 4). This had not been present in 1959 Eight blood cultures were sterile. Because of persistent low-grade fever and the new diastolic murmur the patient was treated with penicillin and streptomycin for suspected subacute bacterial endocarditis His temperature remained slightly elevated during 25 days of antibiotic therapy but there developed no evidence of peripheral embolization or congestive heart failure. The diagnosis of endocarditis was uncertain at the *time of discharge.*

In December 1962, he entered the hospital in congestive heart failure and responded to digitalis and diuretics At this time the blood pressure was 250/130. The heart was enlarged and the diastolic murmur at the apex was again described.

In March 1964 he was readmitted to the hospital in severe congestive heart failure with marked edema, despite antecedent antihypertensive and anticongestive therapy Blood pressure was 200/110, pulse 80 and regular Linear hemorrhages and A V *nicking were seen in the fundi. The point of maximal* cardiac impulse was in the sixth intercostal space in the anterior axillary line. The second heart sound was paradoxically split A grade 4/6 decrescendo, pandiastolic blowing murmur was quite localized to the apex seemed close to the ear and though *markedly reduced during mild inspiration,* was unaffected by changes in position or by the Valsalva maneuver The murmur extended slightly into systole The possibility was suggested that this murmur originated from stenosis of the calcified *coronary artery seen by x-ray A retrograde* aortogram with supravalvular injection of contrast material demonstrated no evidence of aortic insufficiency but showed narrowing of the left anterior descending coronary artery in the region of the previously described calcification narrowing of the circumflex branch and poor filling of the right coronary artery There were no abnormal arteriovenous communications (Fig 5).

The patient did well until readmission to the hospital in September 1964 for treatment of edema and dyspnea. The prominent cooing diastolic murmur was easily noted. After relief of congestive failure, the patient was followed in Cardiac Clinic until the final admission to the hospital, on January 3 1965 which was occasioned by severe relentless precordial pain of 15 hours duration. The vital signs were unchanged. There were distended neck veins and basilar chest râles. Several observers who had previously examined the patient noted a remarkable diminution in intensity of the apical

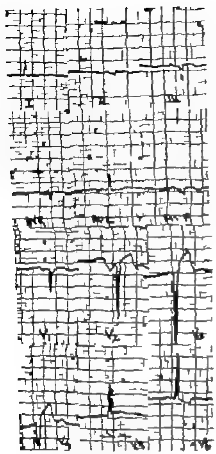

Fig. 6. January 1965, ECG in Case 2 shows Q waves and ST-segment elevations in Leads II, III, AVF, and V_{1-6} that had not previously been present.

diastolic murmur from grade 4/6 to grade 1/6. Peripheral edema and hepatomegaly were present. The ECG showed Q waves and ST-segment elevation in Leads II, III, AVF, and in precordial Leads V_1-V_6 that had not previously been present (Fig. 6). Subsequent ECG's during his 26 days in the hospital showed evolving T wave changes consistent with extensive myocardial infarction involving the inferior and anteroseptal regions. Hematocrit was 25 per cent and stools were guaiac positive. He responded to anticongestive measures and transfusions of packed red cells with diuresis and loss of edema. Nevertheless, the diastolic murmur remained difficult to hear even when the patient had clearly recovered from congestive heart failure. Because of diarrhea and subsequent hypokalemia, digitalis was discontinued, but congestive failure then recurred. He died suddenly during redigitalization. Permission for autopsy could not be obtained.

Discussion

Several characteristics of the decrescendo, diastolic murmur heard in March, 1964, led us to doubt a valvular origin. The circumscribed apical localization of such a loud murmur and its superficiality were findings atypical for aortic valvular insufficiency. The ease with which the murmur disappeared from grade 4/6 intensity with slight inspiration (presumably due mainly to interposition of lung tissue between the heart and chest) suggested that the murmur did not arise from the vasculature of the chest wall. Furthermore, coronary calcification had become evident by x-ray at about the same time as the murmur (neither was present in 1959 and both were present in 1962). It was therefore suggested that flow across an area of coronary stenosis was responsible for the murmur. The diastolic timing was consistent with this interpretation, since proximal coronary blood flow is mainly a diastolic event.[19] The hypothesis was subsequently strengthened by two major observations. (1) Aortic valve regurgitation was practically excluded by a good retrograde aortogram. Certainly, if the regurgitation had been due to bacterial endocarditis or to a dilated aortic root as a result of diastolic hypertension or medionecrosis, the angiogram would not have been normal. (2) At the time of the patient's final admission to the hospital, the intensity of the murmur was markedly reduced concomitant with an acute myocardial infarction. In the absence of postmortem analysis of the exact distribution of coronary vascular pathology, one must speculate that coronary occlusion distal to the stenotic lesion so reduced blood flow at the site of stenosis that the murmur was nearly eliminated. Two other possible explanations for the reduction in murmur intensity at this time were discarded. (1) the continued presence of diastolic hypertension negated the possibility that diminution of the murmur reflected relief of aortic insufficiency previously induced by hypertension;[27] (2) the murmur did not reintensify after relief of congestive heart failure, thereby making it unlikely that diminished flow across an insufficient pulmonic or aortic valve had reduced a murmur previously due to insufficiency of either of these valves.

This case suggests that some diastolic murmurs which are commonly ascribed to aortic root dilatation, as in hypertensive cardiovascular disease, may actually arise

from atherosclerotic coronary artery disease. The localization of such murmurs may not clarify their etiology. Although the diastolic murmur secondary to aortic root dilatation is often heard loudest along the lower right sternal border,[22] it is conceivable that a murmur arising from stenosis of the right coronary artery could be similarly localized to the right sternal border in the same way as a murmur due to a congenital lesion of this artery,[23] thereby mimicking the findings of aortic regurgitation due to aortic root dilatation.

Summary

Two patients with diastolic murmurs resulting from common sequelae of atherosclerotic coronary artery disease are presented. In the first patient, aortic insufficiency resulting from a left ventricular aneurysm was documented antemortem by aortography. Postmortem examination revealed normal aortic valve leaflets. The second patient demonstrated a diastolic murmur due to blood flow through a stenosis of the left coronary artery. The murmur receded when a myocardial infarction occurred in the area of the heart supplied by this artery. Although the murmur suggested aortic insufficiency, there were differentiating features and a competent aortic valve was demonstrated by antemortem aortography.

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REFERENCES

1. Abrams, D. L., Edelist, E., Luria, M. M., and Miller, A. J.: Ventricular aneurysm. A reappraisal based on a study of 65 consecutive autopsied cases, Circulation 27:164, 1963.
2. Wartman, W. B., and Hellerstein, H. K.: The incidence of heart disease in 2,000 consecutive autopsies, Ann. Int. Med. 28:41, 1948.
3. Schlichter, J., Hellerstein, H. K., and Katz, L. H.: Aneurysm of the heart: a correlative study of 102 proved cases, Medicine 33:43, 1954.
4. Dressler, W., and Pfeiffer, R.: Cardiac aneurysm: a report of ten cases, Ann. Int. Med. 14:100, 1940.
5. Parkinson, J., Bedford, D. E., and Thomson, W. A. R.: Cardiac aneurysm, Quart. J. Med. 7:455, 1938.
6. Scherf, D., and Brooks, A. M.: The murmurs of cardiac aneurysm, Am. J. M. Sc. 218:389, 1949.
7. Libman, E., and Sacks, B.: A case illustrating the leucocytosis of progressive myocardial necrosis following coronary artery thrombosis, Am. Heart J. 2:321, 1927.
8. Vakil, R. J.: Ventricular aneurysms of the heart. Preliminary report on some new clinical signs, Am. Heart J. 49:934, 1955.
9. Gorlin, R., Klein, M. D., and Sullivan, J. M.: Prospective correlative study of ventricular aneurysm, Am. J. Med. 42:512, 1957.
10. Klein, M. D., Herman, M. V., and Gorlin, R.: A hemodynamic study of left ventricular aneurysm, Circulation 35:614, 1967.
11. Nordenfelt, O.: The electrocardiogram in chronic aneurysm of the heart, Acta med. scandinav. 102:101, 1939.
12. Abrahams, D. G., Barton, C. J., Cockshott, W. P., Edington, G. M., and Weaver, E. J. M.: Annular subvalvular left ventricular aneurysms, Quart. J. Med. 31:345, 1962.
13. Lewis, T.: Studies of capillary pulsation with special references to vasodilatation in aortic regurgitation and including observations on effects of heating human skin, Heart 11:151, 1924.
14. Gorlin, R., and Goodale, W. T.: Changing blood pressure in aortic insufficiency. Its clinical significance, New England J. Med. 255:77, 1956.
15. Ross, J. R., Epstein, E. J., Criley, J. M., and Ross, R. S.: Hemodynamic effects of severe aortic regurgitation, Brit. Heart J. 26:412, 1964.
16. Kelly, E. R., Morrow, A. G., and Braunwald, E.: Catheterization of the left side of the heart. A key to the solution of some perplexing problems in cardiovascular diagnosis and management, New England J. Med. 262:162, 1960.
17. Petrovsky, B. V.: Surgery for aneurysms of the heart after myocardial infarction, Arch. Surg. 84:397, 1962.
18. Likoff, W., and Bailey, C. P.: Ventriculoplasty: Excision of myocardial aneurysm, J.A.M.A. 158:915, 1955.
19. Dock, W., and Zoneraich, S.: A diastolic murmur arising in a stenosed coronary artery, Am. J. Med. 42:617, 1967.
20. Sabiston, D. C., and Gregg, D. E.: Effect of cardiac contraction on coronary blood flow, Circulation 15:14, 1957.
21. Levine, S. A., and Harvey, W. P.: Clinical auscultation of the heart, Philadelphia & London, 1959, W. B. Saunders Co., p. 291.
22. Ibid. p. 312.
23. Gasul, B. M., Arcilla, R. A., Fell, E. H., Lynfield, J., Bicoff, J. P., and Luan, L. L.: Congenital coronary arteriovenous fistula, Pediat. 25:531, 1960.

Ventricular septal defect and hypoplastic right ventricle

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Ventricular septal defects are frequently associated with other independent anomalies of the heart and great vessels.[1] Under these circumstances, the ventricular septal defect may be readily identified while an associated anomaly such as a patent ductus arteriosus may be overlooked unless specifically sought.[2]

This communication describes the findings in each of two patients with a ventricular septal defect whose postoperative complications may perhaps be attributed to an associated and clinically unrecognized hypoplastic right ventricle.

Case report

Case 1. An 11-month-old American Indian girl was referred for investigation of a cardiac murmur which was first detected at the age of four days. She was the product of a full-term normal pregnancy and there were no siblings. At the age of nine months she was given digitalis and diuretics because of congestive cardiac failure.

On admission, she weighed 5.7 kilograms and appeared ill. The respiratory rate was 80 per minute, and the pulse rate was 180 per minute. There was no cyanosis, anemia, or jaundice, and the liver was palpable two fingerbreadths below the right costal margin. A precordial bulge was not present, and on auscultation a Grade III/VI pansystolic murmur was present maximally in the third interspace at the left sternal border. The second cardiac sound was narrowly split and the pulmonary component markedly accentuated. A soft, early diastolic murmur was audible in the pulmonary area. The lungs were normal.

A roentgenogram of the thorax (Fig. 1) showed marked cardiomegaly with pulmonary plethora suggestive of a left-to-right shunt. The retrosternal space was obliterated, a feature considered to indicate right ventricular hypertrophy. Left atrial enlargement was also present.

The electrocardiogram (ECG) (Fig. 2) showed a mean frontal plane QRS axis of −40 degrees. The tall R and deep Q waves in standard Leads I, aVL, and V_6, and the deep S wave in Lead V_1 suggested the presence of left ventricular hypertrophy. The height of the R waves in Leads V_1, V_2, and V_4, and the equiphasic complexes in Lead V_3 suggested the presence of some right ventricular hypertrophy also. The P waves in standard Leads I, II, and V_1 were peaked with a broad base suggesting right atrial enlargement.

The vectorcardiogram (VCG) (Fig. 2) in the horizontal plane showed a counterclockwise loop

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Fig 1 Roentgenograms of the thorax. Posteroanterior view b lateral view

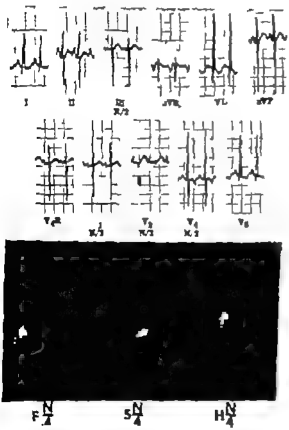

Fig 2 ECG and VCG F Frontal S sagittal and H horizontal plane respectively

with diminution of right ventricular forces, most of the forces being directed to the left and posteriorly In the sagittal plane there was a clockwise loop predominantly above the horizontal axis. I the frontal plane the loop was counterclockwise deviated to the left and superiorly

Table I Synopsis of data obtained during cardiac catheterization

Site of sampling	*Pressure* (mm. *Hg*)	*Oxygen saturation* (*per cent*)
Left subclavian	—	62
Left innominat	—	62
Right innominate	—	62
Superior vena ca a	—	62
Right trium	M = 18	74
Right ventricle	93/0-15	—
Inferior vena cava (high)	—	71
Inferior vena cava (low)	—	70
Left atrium	M = 18	94
Left ventricle	100/0-17.5	95

When the clinical status of the patient had improved, cardiac catheterization was performed the findings are summarized in T ble I Technical dif ficulties prevented advancing the catheter into the pulmonary artery Studies for oxygen values demonstrated an increase in saturation t atrial level. The pressures in the ventricles were virtually identical.

Left ventricular cineangiography showed the presence of a large ventricular septal defect in addition, the right ventricula cavity was noted to be small (Fig 3). A left-to-right sho t was lso demonstrated at atrial level following recirculation of contrast material through the lungs.

The clinical, radiologic, and electrocardiographic features were thought to be compatible with an endocardial cushion defect with shu ting at atrial and entricular levels, and the patient was submitted to operation.

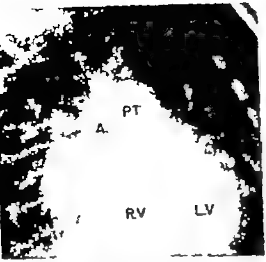

Fig. 3 Left ventricular cineangiogram posterior projection. The hypoplastic right ventricle (R.V.) has been opacified by the passage of contrast material across ventricular septal defect. The size of the right ventricle remained the same in systole and diastole. L.V. Left ventricle. A aorta. P.T. pulmonary trunk.

With the aid of cardiopulmonary bypass, right ventriculotomy was performed and, through this, a large ventricular septal defect was closed with Teflon patch. Following this procedure, the patient was seriously hypotensive, requiring institution of partial bypass several times. While the incision was being closed, cardiac arrest occurred and the patient died despite resuscitative measures.

Necropsy findings. The great arterial vessels were normally related, and the pulmonary venous connections were normal. The right atrial cavity was enlarged and its wall thickened. At the fossa ovalis a septal defect 1½ cm. in diameter was present. The tricuspid ring was narrow and the valve hypoplastic. The right ventricle was 1/3 the size of the left ventricle. A ventricular septal defect, 1.2 cm. in diameter closed with a Teflon patch, was situated below the crista supraventricularis and posterior to the papillary muscle of the conus (Fig. 4). The left ventricle was dilated and its wall measured 1.2 cm. in thickness. From the left ventricular aspect the ventricular septal defect was located below the posterior and right aortic cusps (Fig. 4 b). The left atrium as enlarged and the mitral valve normal. Histologic examination of the lungs showed extensive bilateral atelectasis. The muscular pulmonary arteries showed medial hypertrophy but no intimal changes were present.

Case 2 This case of a 7-year-old boy has been discussed in greater detail previously. His five siblings are well. The clinical, hemodynamic, and radiologic features (Fig. 5) indicated pulmonary hypertension associated with large left-to-right shunt at ventricular level and additional shunt at the atrial level. Because of the features of the scalar and vector ECG (Fig. 6) an endocardial cushion defect was considered to be present. The patient died shortly after closure of the atrial and ventricular septal defects under conditions of cardiopulmonary bypass.

Necropsy revealed that, whereas the inflow portion of the right ventricle was markedly hypoplastic, the infundibulum was dilated and the crista supraventricularis hypertrophied. The ventricular septal defect showed some of the features of the atrioventricular commune type of defect, but the atrial septal defect was at the fossa ovalis. Histologic examination of the lungs showed fibrous thickening of the intima and elastosis of the media of the large muscular pulmonary arteries medial hypertrophy and occasional plexiform lesions were observed in the small muscular arteries.

Comment

Congenital hypoplasia of the right ventricle is an uncommon cardiac malformation, usually encountered in association with other conditions such as tricuspid atresia,[4] congenital tricuspid stenosis,[5] and pulmonary atresia with intact ventricular septum. We have been able to find reports of only ten cases, proved at necropsy or at operation, of hypoplastic right ventricle unassociated with intrinsic valvular abnormalities.[1,3-6] Of the ten patients, there were two families in which siblings were involved each family having two patients with this anomaly. A patent foramen ovale or atrial septal defect was present in each of these cases, but in none was there a proven co-existing ventricular septal defect.

The hemodynamic, electrocardiographic, and clinical features of hypoplastic right ventricle associated with atrial septal defect or patent foramen ovale but with an intact ventricular septum have been well reviewed by Sackner and associates. The hypoplastic right ventricle offers an obstruction to its diastolic filling and in the presence of an interatrial communication a right-to-left shunt with central cyanosis will occur. Left ventricular hypertrophy and dilatation are a reflection of the extra load borne by the left ventricle as a result of the right-to-left shunt at atrial level. The restriction of diastolic filling of the right ventricle is further manifested by large "a" waves in the jugular venous pulse. This picture is similar to that of tricuspid atresia, and the ECG may be indistinguishable, viz. left axis deviation right atrial enlargement, and left ventricular hypertrophy or absence

Fig 4 Necropsy specimen Hypoplastic right ventricle (*R.V.*) and ventricular septal defect (*D*). A probe lies i the tricuspid orifice (*T*) which is narrow *P V* Pulmonary val *b* Left ventricle (*L.V.*). The ventricular septal defect (*D*) has been closed w th a Teflon patch *A* Aorta.

Fig 5 Roentgenogram of thorax taken at the age of seven years. Posteroanterior view *b* lateral view Sternal prominence. (*From Davach and associates* AM. HEART J *67*:271 *1967* *reproduced with permission.*)

of right ventricular potentials in the precordial leads.

When a hypoplastic right ventricle is associated with a ventricular septal defect, however the picture is strikingly different as illustrated in the two cases of this report. Each case presented clinically as an example of large ventricular septal defect with severe pulmonary hypertension car diac failure and repeated episodes of pneumonia. Cardiac catheterization dem onstrated high right atrial pressures and pulmonary arterial pressures at systemic levels. Large left-to-right shunts were demonstrated by oximetry or by cineangiography The high right atrial pressures may be related to cardiac failure, but may also be a reflection of the increased filling resistance of the hypoplastic right ventricle.

The systemic saturations were 95 and 94 per cent in Cases 1 and 2 respectively levels slightly lower than those usually observed in unsedated children in this

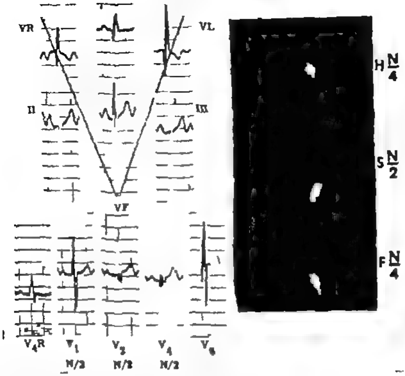

Fig. 6. Electrocardiogram showing left axis deviation (−75°) and incomplete right bundle branch block. The P waves in Leads II and V are abnormally tall with a broad base, suggesting right atrial enlargement. The predominant R wave in Lead V_{4R} and the positive T wave in Lead V indicate right ventricular hypertrophy. The deep Q wave in lead V suggests left ventricular hypertrophy in addition. The vectorcardiogram shows a counterclockwise QRS loop in the frontal plane. The clockwise inscription of the QRS loop in the left sagittal plane indicates right ventricular hypertrophy. In the horizontal plane this is confirmed by the clockwise inscription of the vector loop with significant rightward and posterior forces. The terminal electrical forces are delayed. (From Davachi and associates: Am. Heart J. 67:271, 1967, reproduced with permission.)

laboratory. The possibility exists that a small right-to-left shunt was present. In addition, this may have been caused by blood flowing from the right ventricle to the left during diastole. The magnitude of such a right-to-left shunt at ventricular level may be masked by large volumes of highly saturated blood in the left ventricle, resulting from the large left-to-right shunt.

In each case, the ECG's suggested that the ventricular septal defect was of the atrioventricular commune type. In Case 2, the ventricular septal defect exhibited some of the anatomical features of the atrioventricular commune type of defect. In Case 1, however, the ventricular septal defect was of the usual infracristal variety. It is possible, therefore, that the left axis deviation is related to the hypoplastic right ventricle rather than to the type of ventricular septal defect present, especially since the same electrocardiographic phenomenon may be observed with hypoplastic right ventricle and intact ventricular septum. Of interest is the fact that both cases demonstrated the presence of right ventricular forces on the ECG and VCG. Indeed, in Case 2, the findings were suggestive of predominant right ventricular hypertrophy, whereas in Case 1, the electrocardiographic findings were suggestive of biventricular hypertrophy. It is noteworthy that, while both cases had marked hypoplasia of the inflow portion of the right ventricle, the infundibulum was more hypertrophied in Case 2 than in Case 1. This anatomic feature might explain the differences in the ECG's of the two cases.

From the therapeutic point of view, this condition poses a difficult problem

With extreme degrees of hypoplasia of the right ventricle closure of the ventricular septal defect will result in acute right ventricular inflow obstruction and in the presence of an atrial septal defect or patent foramen ovale a transatrial right-to-left shunt may become established and an inadequate pulmonary blood flow will result. Closure of the ventricular and atrial septal defects in conjunction with performance of a superior vena caval-pulmonary arterial anastomosis would not be a feasible procedure to increase the pulmonary blood flow under these circumstances because of the pulmonary hypertension. Resection of a portion of the muscle of the right ventricle may increase the capacity of this chamber sufficiently to allow closure of the defects.[11] With lesser degrees of hypoplasia of the right ventricle, however closure of the ventricular septal defect, leaving the atrial septal defect open or actually enlarging it, may be a more practical procedure that awaits proof

The postoperative demise of these patients makes a diagnostic awareness of this entity imperative. In a clinical picture of a ventricular septal defect, the presence, additionally of a hypoplastic right ventricle may perhaps be suggested by the absence of the characteristic left parasternal thrust of right ventricular hypertrophy encountered in patients with ventricular septal defect and pulmonary hypertension. It is noteworthy that there was nothing to suggest hypoplasia of the right ventricle in the thoracic roentgenograms. The lateral views of both patients showed obliteration of the retrosternal space a finding probably representing the state in which the enlarged left ventricle pushed the right ventricular infundibulum and enlarged pulmonary trunk forward against the anterior thoracic wall.

The features of hypoplastic right ventricle in these cases are essentially those of a large ventricular septal defect with pulmonary hypertension and perhaps a left-to-right shunt at atrial level associated with the characteristic ECG of an endocardial cushion defect It should be noted that the usual infracristal type of ventricular septal defect is occasionally associated with similar electrocardiographic features[12] and that endocardial cushion defects are not always accompanied by mitral and tricuspid incompetence. These conditions may thus closely resemble ventricular septal defect with a hypoplastic right ventricle. When a suspicion of hypoplasia of the right ventricle is raised right ventriculography is indicated as having the greatest potential to test this point

Summary

Two patients with hypoplastic right ventricle who died following closure of an associated ventricular septal defect are described. Both cases presented with large left-to-right shunts and pulmonary hypertension. In each case, the diagnosis of an endocardial cushion defect was suggested by the ECG The presence of the hypoplastic right ventricle was not suspected on electrocardiographic or vectorcardiographic grounds, since both showed the presence of right ventricular forces probably generated from the outflow portion of the right ventricle. Thoracic roentgenograms were not diagnostically helpful. Since the condition closely resembles endocardial cushion defect unaccompanied by incompetence of the atrioventricular valves, or the occasional case of infracristal ventricular septal defect with an electrocardiogram similar to the aforementioned condition the use of selective right ventricular angiography under these circumstances may be of diagnostic assistance in identifying the presence of a hypoplastic right ventricle.

REFERENCES

1. Girod, D A., Raghib, G., Adams, P Jr Anderson, R. C., Wang Y and Edwards, J E. Cardiac malformations associated with ventricular septal defect, Am. J Cardiol. 17 73 1966.
2. Elliott, L. P Ernst, R. W Anderson, R. C., Lillehei, C. W and Adams, P Jr Silent patent ductus arteriosus in association with ventricular septal defect. Clinical, hemodynamic, pathological, and surgical observations in forty patients, Am. J Cardiol. 10:475 1962.
3. Davachi, F., Moller J H., Amplatz, K., Chesler E., Korns, M. E., and Edwards, J E.: Atrial and ventricular septal defects with hypoplasia of right ventricle, Am. Heart J 74:271 1967
4. Keith, J D Rowe, R. D., and Vlad, P : Heart

disease in infancy and childhood, Ed. 2, New York, 1967 The Macmillan Company p. 434

5 Medd, W E., Neufeld, H. N Weidman, W H., and Edwards, J E. Isolated hypoplasia of the right ventricle and tricuspid valves in siblings, Brit. Heart J 23:25 1961

6. Davignon, A. L., Greenwold, W E., DuShane, J W and Edwards, J E. Congenital pulmonary atresia with intact septum. Clinicopathologic correlation of two anatomic types, Am. Heart J 62:591 1961.

7 Cooley R. N Sloan R. D Hanlon, C. R and Bahnson, H. T Angiocardiography in congenital heart disease of cyanotic type. II Observations on tricuspid stenosis or atresia with hypoplasia of the right ventricle Radiology 54:848, 1950.

8. Fay J E., and Lynn, R. B. Isolated right ventricular hypoplasia with atrial septal defect, Canad. M A. J 88:812, 1963.

9 Gasul, B M., Weinberg, M J Luan, L. L., Fell, E. H., Bicoff J and Steiger Z. Superior vena cava-right main pulmonary artery anastomosis. Surgical correction for patients with Ebstein anomaly and for congenital hypoplastic right ventricle J.A.M.A. 171 1797 1959

10. Sackner M. A., Robinson, M. J Jamison, W L., and Lewis, D H. Isolated right ventricular hypoplasia with atrial septal defect or patent foramen ovale Circulation 24 1388, 1961

11 Williams, J C. P Barratt Boyes, B G and Lowe, J B Underdeveloped right ventricle and pulmonary stenosis, Am. J Cardiol. 11 458, 1963

12. Char F Adams, P J and Anderson, R. C. Electrocardiographic findings in one hundred verified cases of ventricular septal defect, Am. J Dis. Child. 97:48, 1959

Multiple aneurysms of the coronary arteries

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In 1963, in a review of the literature, Daoud and associates[1] collected 89 cases of aneurysm of the coronary arteries, all diagnosed post mortem. Since then 10 cases have been reported.[2-4]

In 1958 Munkner and co-workers[5] reported a case diagnosed during life. This was a congenital coronary aneurysm in an 8-year-old child diagnosed by coronary angiography.

In this report, a case of multiple coronary artery aneurysms diagnosed by cinecoronary angiography is described and is believed to be the second instance of diagnosis during life.

Case report

E. S., a 43-year-old Negro man, was admitted to the hospital following a bout of retrosternal chest pain, which woke him from sleep and was accompanied by profuse sweating. The pain was described as severe and sharp, without radiation, and lasted about one hour until relieved following Demerol. He had no previous history of chest pain other than soreness in the left precordial region which occurred intermittently 15 minutes after meals and lasted 10 to 15 minutes. There was no relation to exertion or cold weather. He admitted intermittent epigastric discomfort after meals relieved by food. He denied exertional dyspnea and orthopnea and had no other symptoms. He smoked four to five cigars daily. He had no previous illnesses, and there was no personal or family history of cardiovascular disease, diabetes, or hyperlipemia.

Physical examination revealed a mildly obese Negro man, weighing 180 pounds. His pulse was normal and his blood pressure was 110/76. The heart was not enlarged clinically. On auscultation the heart sounds were normal, there were no added sounds but there was a Grade II/VI ejection systolic murmur at the apex. There were no signs of congestive heart failure, the peripheral pulses were normal, and physical examination otherwise was normal. Chest x-ray showed a normal heart size (CTR 14.5/32) and normal lung fields. A gastrointestinal series was normal. The electrocardiogram (ECG) of Sept. 19, 1966, showed an early repolarization pattern with S-T elevation and T inversion over the lateral precordial leads but was otherwise within normal limits. Laboratory studies showed hemoglobin 15.6 Gm. and the white blood count (WBC) was 9,900 with normal differential count. VDRL was negative. Serum electrolytes, proteins, blood urea nitrogen (BUN), and liver function tests were normal. Urinalysis and serial enzyme studies were normal. The fasting serum was lipemic with cholesterol (350 mg. per cent), and a two hour postcibum blood glucose was 132 mg. per cent.

Subsequently, while in the hospital, he had two further episodes of chest pain at rest lasting one half hour and one hour, respectively, and relieved by administration of Demerol and oxygen. Further enzyme studies were normal, but the ECG dated

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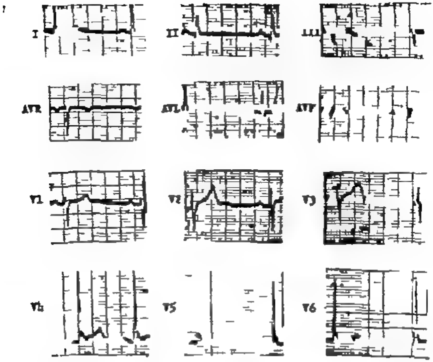

Fig. 1. An ECG taken on Sept. 27, 1966.

Fig. 2. Left oblique view of the right coronary artery.

Fig. 3. Right oblique view of the left coronary artery.

Table I. Coronary arteriograms

Atherosclerotic heart disease (ASHD) alone		90
Atherosclerotic heart disease with other heart disease		36
ASHD with rheumatic heart disease	20	
ASHD with cardiomyopathy	7	
ASHD with miscellaneous	9	
Other cardiac diseases without ASHD		49
Normal heart		25
Total		200

Sept. 27, 1966, showed upright T waves over the precordial leads and T inversion in Leads III and aVF which suggested inferior wall ischemic changes. This pattern persisted in subsequent tracings (Fig. 1).

One month after admission, cardiac catheterization and cine-coronary angiograms were performed. There was a large predominant right coronary artery. Throughout its length, the vessel showed marked variations in caliber. The proximal portion of the vessel showed general dilatation with localized fusiform aneurysms. On the inferior wall there were four fusiform aneurysms separated by short segments of normal caliber. The diameter of the aneurysms varied between three and four times the normal caliber of the vessel. The proximal branch to the right atrium also showed a single aneurysm close to its origin and did a major branch further distally (Fig. 2).

The left coronary artery showed some generalized dilatation proximally with two fusiform aneurysms in the anterior descending branch and considerable variations in caliber further distally. However, the appearance was not as striking as the right coronary artery (Fig. 3).

Both vessels showed irregularities of the wall suggesting moderate diffuse atherosclerotic changes but there were no obstructive lesions.

Discussion

Over a two year period from February 1965, 200 cine-coronary angiograms were performed at the Veterans Administration Hospital, Cleveland, Ohio, and this is the only instance of a coronary artery aneurysm (Table I).

Although atherosclerosis is the most common cause of coronary aneurysm,[1] syphilis, periarteritis nodosa, embolism, bacterial endocarditis, congenital defect, and trauma have been implicated. In the present case the association of chest pain, electrocardiographic changes, lipemic serum with high cholesterol and abnormal glucose tolerance test, and the angiographic appearances all suggest that atherosclerosis is the underlying cause. The symptomatology of coro-

nary aneurysm is not specific. Symptoms and signs are usually referable to the primary disease[1] and for this reason antemortem diagnosis is rare. As in Munkner's case[6] the diagnosis was made by coronary arteriography. In Barclay's case, in retrospect, the diagnosis might have been considered from the calcification seen on the plain chest x-ray film.

Prognosis is usually poor. Death usually occurs suddenly from rupture or myocardial infarction and treatment is not available.

Summary

This report concerns a 48-year-old Negro man with angina, electrocardiographic changes suggesting inferior wall ischemia and a lipemic serum with high cholesterol. Cine-coronary angiogram disclosed multiple fusiform aneurysms mainly of the right coronary artery. It is believed that this is the second case of coronary aneurysm diagnosed in life.

REFERENCES

1. Daoud, A. S., Pankin, D., Tulgan, H., and Florentin, R. A.: Aneurysms of the coronary artery. Report of ten cases and review of literature, Am. J. Cardiol. 11:228, 1963.
2. Bertelsen, S., and Lindahl, A.: Aneurysms of the coronary arteries: report of two cases, Acta med. scand nav. 175:589, 1964.
3. Naltandian, R. M., and Chason, J. L.: Intramural dissecting hematomas in normal or otherwise unremarkable coronary arteries—A rare case of death, Am. J. Clin. Path. 43:348, 1965.
4. Brody, G. L., Burton, J. F., and Zawadzki, E. S.: Dissecting aneurysms of the coronary artery, New England J. Med. 273:1, 1965.
5. Barclay, C. C., Glenney, W. R., and Hobbs, R. E.: Aneurysms of the coronary artery. A case report, Am. J. Roentgenol. 91:1315, 1964.
6. Munkner, T. M., Petersen, O., and Vesterdal, J.: Congenital aneurysm of the coronary artery with an arteriovenous fistula, Acta Radiol. 50:333, 1958.

Clinical pathologic conference

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Clinical abstract

This 12-year-old boy was first seen at Duke Hospital at the age of two years because of mild cyanosis and a heart murmur which were detected at one year of age. He was followed as an outpatient with moderate cyanosis on exertion and mild exercise intolerance. At the age of 12 he was admitted for preoperative cardiac catheterization because of increasing symptoms.

Physical examination revealed mild growth retardation and mild generalized cyanosis. Chest examination revealed a right ventricular precordial heave accompanied by a Grade IV harsh, holosystolic murmur which was loudest in the third left interspace. The second sound was single. There were no diastolic murmurs.

The electrocardiogram (ECG) (Fig. 1) indicated right ventricular hypertrophy. The cardiac x-ray (Fig. 2) revealed a normal sized heart, a concavity in the area of the main pulmonary artery, and generalized diminution in pulmonary vascular markings. Laboratory studies revealed a hemoglobin of 16 Gm. per cent.

Cardiac catheterization demonstrated a systemic pressure in the right ventricle with evidence of both valvular and infundibular pulmonic stenosis on the pullback pressure tracings from the pulmonary artery to the right ventricle. Cineangiocardiography demonstrated an adequate sized main pulmonary artery with apparent narrowing at the origin of both right and left pulmonary arteries (Fig. 3). Retrograde aortogram demonstrated quite prominent bronchial circulation to the superior portion of both lungs. The peripheral arterial oxygen saturation was 89 per cent.

He underwent corrective cardiac operation which included closure of the ventricular septal defect with a Teflon patch and widening of the outflow tract of the right ventricle with a pericardial graft. During cardiopulmonary bypass, an abnormally large quantity of blood was noted to return to the left heart while the ventricular defect was being closed. Immediately following successful cardiopulmonary bypass, sanguineous fluid exuded from the endotracheal tube and the patient was considered to have developed pulmonary edema. Left atrial pressure was measured and found to be normal (12/4 mm. Hg). Intravenous digoxin was administered, the chest closed, and the patient returned to the recovery room. His postoperative course was characterized by labored breathing and he was maintained on an Engstrom respirator. Constant high oxygen inhalant gaseous mixtures were utilized; however, cyanosis persisted with the arterial pO_2 ranging from 50 to 62 mm. Hg. No heart murmurs were audible postoperatively. From the second to the fifth postoperative day the chest roentgenogram showed increasingly severe parenchymal infiltration of both lung fields (Fig. 4). His course was steadily downhill until he died on the fifth postoperative day.

Discussion

DR. CANENT. The clinical features, physical findings, and cardiac catheterization data all were consistent with typical tetralogy of Fallot in this child. We followed him as an outpatient for quite a few years and considered that the severity of his exercise limitation was greater than one usually sees associated with minimal cyanosis.

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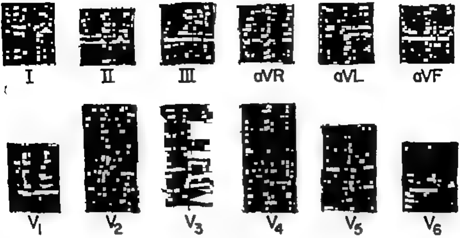

Fig. 1. Preoperative ECG at 11 years of age.

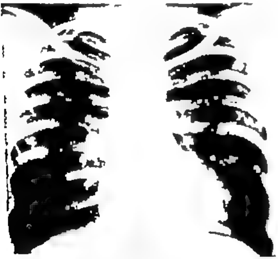

Fig. 2. Preoperative chest roentgenogram. The findings are typical of tetralogy of Fallot with normal-sized heart, prominence of the right ventricle and concavity in the area of the main pulmonary artery. The aortic arch was on the left side. The pulmonary vascular markings were diminished with slight prominence in the area of the proximal left pulmonary artery.

At the conclusion of cardiopulmonary bypass, we were in the operating room with Dr Sabiston and were quite perplexed as to the severity of pulmonary edema in the presence of a normal left atrial pressure. The surgical repair seemed quite excellent and there was no evidence of left heart failure as a factor to generate pulmonary edema (normal left atrial pressure). During the postoperative state the problems were entirely pulmonary. We were especially impressed with the definite sensation of stiffness of the lung that one could appreciate when attempting to inflate his lungs during his last two days of life. The gradually increasing stiffness of the lungs was reflected also by the elevation of pressure which was required for the respirator to move air into the lungs during this time.

DR. LESTER. There are several prominent roentgenographic features that should be emphasized. The cineangiocardiograms demonstrated right ventricular infundibular stenosis, narrowing of the pulmonary valve, and supravalvular narrowing at the bifurcation of the pulmonary artery. There are also segments demonstrating coarctation of the pulmonary artery to the right upper lobe, as well as of a branch of the left pulmonary artery. These findings are frequently associated with tetralogy of Fallot. The right ventricular injection showed a right-to-left shunt directly into the aorta and a left ventricular injection showed a left-to-right shunt across the defect. The aortogram was most interesting. The aorta was large, as commonly seen in tetralogy of Fallot. There was a rich plexus of bronchial arteries (Fig. 3) which were much more prominent than one usually sees in a patient with minimal cyanosis clinically.

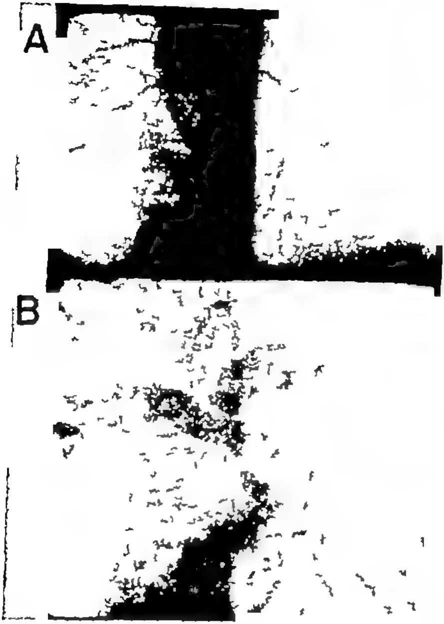

Fig. 3. Cineangiocardiographic findings. (*A*) The retrograde aortogram demonstrated the rich plexus of bronchial arteries as shown above. (*B*) Right ventricular cineangiocardiogram demonstrated infundibular and valvular stenosis with apparent supravalvular narrowing at the bifurcation of the pulmonary artery. At operation and necropsy no evidence of coarctation of the pulmonary arteries was present.

It is my impression that the prominent return of blood to the left heart during cardiopulmonary bypass was secondary to these vessels. This increased pulmonary flow via the bronchial arteries during cardiopulmonary bypass could have been of sufficient magnitude to produce pulmonary edema in the presence of a normal left atrial pressure postoperatively. Postoperatively, the persistent cyanosis and pulmonary edema fall into a group of symptoms comprising the postperfusion syndrome. This is characterized by cyanosis, poor oxygen exchange, and transudation of blood elements into the alveoli resulting in pulmonary edema with alveolar-capillary block as described by Baer and Osborn.[3] They point out that one cause of this phenomenon is the positive surge of pulmonary capillary blood during or at the end of perfusion when the blood flow from the bronchial arteries is drained

A

B

Fig. 4. Progressive pulmonary parenchymal changes postoperatively. (*A*) Extensive parenchymal infiltrates of the lungs are indicated in the chest film on the third postoperative day. (*B*) Further progression of the infiltrates throughout both lung fields, especially on the right, were evidenced on the fourth postoperative day shortly prior to the patient's death. Respiration was maintained via the tracheostomy by means of an Engstrom respirator. Concomitant with the progressive pulmonary changes evidenced on the chest films, increasing pressure levels were required of the respirator to maintain respiration.

into the left atrium and there is no egress of this blood from the heart during the final phase of aortic occlusion.

The sequential chest films taken just prior to death show extensive and progressive infiltrates throughout both lung fields (Fig. 4). Oxygen toxicity is rather appealing to me as a partial explanation of what happened to this patient postoperatively. According to DuBois, high oxygen content in the presence of blockage of the alveoli results in exudation of blood elements from the vascular bed into the alveolar spaces, thus causing alveolar

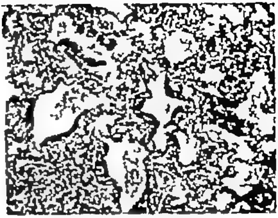

Fig. 5. Section of lung. Note the capillary congestion, edema, focal atelectasis, and prominent hyaline membranes. (Hematoxylin and eosin. ×100.)

capillary block. The immediate postoperative film looked good except for a mild pneumothorax which cleared. The subsequent films showed progressive lung infiltration. In summary, I think this child had tetralogy of Fallot with pulmonary valvular and infundibular stenosis with stenosis of some of the branches of the pulmonary artery. I think the operation as described was successful and that death resulted from pulmonary edema and the attendant physiologic abnormalities in the postoperative state.

DR. SPACH: Consideration of the distribution of the bronchial circulation terminal connections to the pulmonary arterial versus pulmonary venous side of the capillary bed may be of considerable importance here. This distribution can vary quite a bit in normal and abnormal situations. Dr. Ivan Brown has frequently showed us that by sampling from a peripheral pulmonary artery one can find considerable increase in oxygen saturation as compared to the main pulmonary artery. This phenomenon would be most easily explained by bronchial flow into the distal pulmonary arterial branches rather than reflux in a retrograde fashion through the capillaries. Also, with the advent of x-ray magnification techniques, it may become feasible to study the details of bronchial distribution in patients in the not too distant future.

DR. SABISTON: During the operation this patient had a small pulmonary artery, infundibular and valvular pulmonary ste-

nosis, and a ventricular septal defect as shown by the cineangiocardiogram. However, we did not identify any stenotic lesions of the distal pulmonary arteries. Also at the time of autopsy no coarctation of the pulmonary artery was seen. From our standpoint, we were unable to state whether or not the pulmonary problems resulted from the postperfusion lung or whether the ultimate cause of death could be related to oxygen toxicity. However, the arterial pO_2 persisted at low levels and it was thought best to administer rather high levels of oxygen since the arterial pO_2 continued to remain at low levels.

DR. HACKEL. The major abnormalities found on postmortem examination involved the heart and lungs. The heart weighed 250 grams, which is somewhat large for a small child of 12 years. The changes of tetralogy of Fallot were present and included (1) right ventricular hypertrophy with the right ventricular wall (1.0 cm.) being thicker than that of the left ventricle (0.8 cm.), (2) a ventricular septal defect in the region of the septum membranaceum which was well covered by an intact graft of synthetic material, (3) dextroposition of the aorta, and (4) pulmonary stenosis. The pulmonary outflow tract was small but had been widened with a pericardial graft which extended into the proximal pulmonary artery. This was intact and the vessel was patent. There was no evidence of multiple pulmonary emboli. Microscopic sections of the myocardium were normal except for rare foci of minimal necrosis.

The lungs were firm, bluish-red, and heavy, weighing 600 grams on the right and 500 grams on the left. Small thrombi occluded pulmonary arterial branches of the right upper and lower and left upper lobes, but no gross evidence of infarction was present. Microscopically the lungs showed edema, focal atelectasis, focal intravascular hemorrhage, and marked capillary congestion (Fig. 5). In places, the capillaries were remarkably prominent and had the appearance described by Pratt[4] as characteristic of the changes caused by hyperoxia. This is apparently due to proliferation of the capillaries much like granulation tissue, so that in places they extend into the lumina of alveolae. In addition, prominent hyaline membranes lined many alveoli. This, too, is a change which has been commonly described in patients subjected to prolonged oxygen inhalation. Perhaps Dr. Saltzman would care to comment on these changes as related to oxygen therapy.

DR. SALTZMAN. In this patient, there was progressive cardiorespiratory deterioration prior to the sustained therapeutic use of high oxygen tensions. Inhalation therapy became necessary because of decreasing pulmonary gas exchange so that even exposure to 100 per cent oxygen maintained the arterial pO_2 at an unsatisfactory low level of 50 mm. Hg. Despite all efforts, the patient continued to deteriorate and died. In the lungs, the autopsy findings of congestion, hyalin membrane formation, and edema are compatible with the deteriorating clinical course of this child after the operation. The observed capillary proliferation may be a more specific reflection of oxygen toxicity, but in this case the environmental gas exposure seems more appropriate as an accessory rather than primary factor in the pathogenesis of the postmortem pulmonary picture.

In this patient, oxygen therapy became necessary to sustain life in the face of progressive cardiorespiratory failure causing severe hypoxia. At the same time, protracted exposure to high oxygen tensions aggravated, in all probability, the pathologic response of the lungs and accelerated the deterioration of respiratory gas exchange. In view of our limited knowledge of oxygen effects, it is clear that we will progress beyond this therapeutic dilemma only after more basic information is acquired.

REFERENCES

1. Levin, A. R., Boineau, J. P., Spach, M. S., Canent, R. V., Jr., Capp, M. P., and Anderson, P. A. W.: Ventricular pressure-flow dynamics in tetralogy of Fallot, Circulation 34:4, 1966.
2. Baer, D. M., and Osborn, J. J.: The postperfusion pulmonary congestion syndrome, Am. J. Clin. Path. 34:442, 1960.
3. DuBois, A. B.: Oxygen toxicity, Anesthesiology 23:473, 1962.
4. Pratt, P. C.: The reaction of the human lung to enriched oxygen atmosphere, Ann. New York Acad. Sc. 121:809, 1965.

Fundamentals of clinical cardiology

Testing in hypertension

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The physician today is frequently confronted with the decision as to how much testing to carry out in the patient who comes to him and is found to be hypertensive. It is needless to reiterate here that a good history including the family history and physical examination is of basic clinical importance and will often serve to suggest the possibility of renovascular hypertension, pheochromocytoma, or essential hypertension among other varieties. Some physicians prefer to do nothing but this, together with simple laboratory procedures, such as urine analyses, blood count, and blood urea nitrogen, and then treat with drugs. If the patient is resistant to treatment or difficult to manage, they then resort to more extensive testing. Since at least 80 per cent or more of the patients will be in the essential category, this procedure is not too illogical and by and large produces fairly good results. It is more expedient, however, than desirable and in many cases more complete analysis is not only desirable but necessary. We propose to define some of the problems that arise with reference to decisions as to how far to go with testing.

Ideally, every hypertensive patient as part of his "work up" should at least have urine analysis, urine culture and colony count if indicated, complete blood count, sedimentation rate, serum cholesterol, blood urea nitrogen, fasting blood sugar, serum uric acid, sodium, potassium, chloride, and carbon dioxide content and possibly calcium and phosphorus, also electrocardiogram (ECG) and chest x-ray. Some physicians would add serum protein analysis and protein-bound iodine or a T test as well. In addition, a urinary catecholamine metabolite (CM)[2] test and a rapid-sequence or timed intravenous pyelogram (IVP)[4] should be part of every hypertensive "work up."

In our laboratory, the CM test, a urinary chromatoelectrophoretic assay for the combined metanephrines and 3-methoxy-4-hydroxyphenylethylene glycol, is routinely used because a large number of such tests can be carried out simultaneously. If the test is positive or even suspicious, we do a Pisano test for metanephrines and also a vanillylmandelic acid test. Our record thus far has been spotless in identifying pheochromocytoma and in rejecting other types of hypertension for operation.

Cushing's syndrome, which is often associated with some hypertension, is usually not a difficult clinical diagnosis and its

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presence can be confirmed or denied by testing the urine and/or blood for 17 hydroxycorticoids and 17 ketosteroids.[6] If the hypertension is severe in such cases testing for multiple causes might be indicated.

The rapid sequence IVP is done differently by different radiologists. Some simply inject and take films at 1, 3, 5, 10, and 20 minutes, or more frequently.[7] Others do washout studies by means of mannitol,[8] mercurial, or water diuresis. It is uncertain whether these refinements add very much to the ordinary rapid-sequence IVP which will miss about 15 per cent of renovascular cases.[1] One thing to look for is a difference in length of the kidneys, 1 cm. or more being significant, except that the right is usually slightly larger than the left. The other is any difference between the two kidneys in the time of appearance of the dye or in its concentration in any of the films. If there is suspicion on these grounds or on clinical grounds alone, such as the presence of a significant bruit among other factors, aortogram is the next step. The preferred technique for aortogram is now almost universally the Seldinger technique via the femoral artery.[11] If there is severe peripheral arteriosclerosis, however, translumbar aortogram may be more desirable.[12]

Suppose that a positive lesion is found in the renal artery. What is the next step? The first determination to make is whether the condition is amenable to operation. Many factors enter into this. There may be previous or associated cerebrovascular or coronary occlusions. Both renal arteries may be severely involved and not amenable to repair or bypass. The patient may be very uremic, or may refuse operation, etc. On the positive side for operation would be a short history of the disease, severe hypertension, and resistance to medical therapy, among other considerations.[3]

If it should be decided that an operation might be feasible, the question must then be raised as to whether it would be efficacious in reducing the blood pressure. At this point, many groups would carry out the tests described by Howard and co-workers,[1] or by Stamey and co-workers,[13] and renal vein renin[1] tests with a femoral vein catheter. Other tests are available here if doubt remains, such as radioactive renogram,[7] sensing of a bruit and of diminished pulsation by a ureteral catheter,[14] renal hemodynamic test,[14] and others[19-21] which are still experimental. There are some conditions under which the radioactive renogram becomes more important, for example, if the patient is sensitive to Diodrast.

Several additional tests are now available to predetermine the efficacy of an operation. Some of these are still experimental but they will, in our opinion, come into further use. These are all tests for essential hypertension. The oldest of these is the cold pressor test[22] which is really a measure of the reaction of the patient's blood pressure to pain.[23] The extent of this reaction is usually due to change in peripheral resistance[24] but can be due to change in cardiac output only. What is more, there is much overlapping in the test between patients with essential hypertension, those with anxiety only, and those with renal hypertension who are anxious. It is, however, still used in many laboratories. Another test is the angiotensin infusion test (AIT)[25] which has the advantage of simplicity and is a crude measure of vascular reactivity. It is used in some laboratories as a screening test to separate renovascular from essential hypertension. A third test is the digital vascular reactivity test with either angiotensin[26,27] or l-norepinephrine (NE)[26,27] as the testing substance. This test is older than the AIT and more elaborate, but is always positive in essential hypertension.[28] A third test which has just been introduced is the apparent NE secretion rate.[29] This consists of giving a single injection of tritiated NE and measuring the specific activity of normetanephrine in the urine excreted during the subsequent 24 hours.

These last three tests are less familiar than the others and deserve further consideration. The reason for their use is not merely to screen out renovascular cases but particularly to pick out cases in which renal disease is combined with essential hypertension. This occurs in several situations. It has been shown, for example, that most cases of chronic pyelonephritis with hypertension occur in reality in patients with essential hypertension complicated

by pyelonephritis.[30-32] Nephrosclerosis is a major complication of essential hypertension[33] as is atherosclerosis with atherosclerotic obstruction of the renal artery or arteries.[34] Chronic glomerulonephritis, lupus nephropathy, diabetic nephropathy and other types of renal disease may also occur in patients with underlying essential hypertension possibly more commonly than in patients without essential hypertension.

In perusing some of the surgical literature,[35] one is sometimes left with the feeling that the major cause of failure in renovascular surgery is involvement of the opposite kidney by nephrosclerosis due to the hypertension initiated by the kidney with the renal arterial lesion. Although this undoubtedly occurs, another equally or perhaps even more important cause of failure is the association of renovascular with essential hypertension[36,37] both of which are responsible for nephrosclerosis in the opposite kidney if this exists. These tests may serve to separate out such factors in advance of operation and identify them. One must now ask how reliable they are.

The angiotensin infusion test requires only a blood pressure cuff and angiotensin II. It has the disadvantage of measuring responsiveness of only the blood pressure disregarding the cardiac output factor. In addition, baroreceptor effects are not blocked in the test.[38] Despite these disadvantages, the test may differentiate with considerable overlapping between renal and essential hypertension although even this is disputed.[39-41] The theoretical basis of the test which involves tachyphylaxis to angiotensin produced endogenously is also disputed.[39,41,42]

In the digital vascular reactivity test[36,37] baroreceptor and other reflex factors are blocked by indirect heating and ganglion blockade. Pressure and flow are measured in a restricted part of the circulation under perhaps greatest sympathetic nervous control, namely, the digital arteriovenous anastomoses. The calculation of the work of vasoconstriction also takes into account such factors as critical closing pressure and/or change in intravascular apparent viscosity, venous pressure, intravascular arterial pressure, etc.[43,44] The test is always positive in essential hypertension. Its major disadvantage is the length of time required for each test (about two to three hours). There are, however, other disadvantages. It cannot, for example, be used in patients with pheochromocytoma. Sodium retention increases reactivity,[45] and this may be present to some degree in renal hypertension, thus causing overlapping. It is therefore weakly but definitely positive in primary hyperaldosteronism.[46] Glucocorticosteroids also make the test positive if given over a prolonged period of time[46] and it is positive in Cushing's syndrome.[7]

For all these reasons, a biochemical test for essential hypertension would be most desirable. The development of such a test has been an aim of ours for several years. The first such test devised in our laboratory was developed by Wolf and associates[1] in 1961. It consisted of measuring the disappearance rate in the plasma of I[131] labeled angiotensin. The disappearance rate was definitely slower in patients with essential hypertension, but the technique was hardly practical for extensive use since it required multiple determinations of a curve and repeated labeling of the angiotensin, etc. Each labeled batch had to be tested to be sure that the angiotensin had not been altered, and it was not clear whether renal hypertension could be differentiated from essential hypertension. Wolf and associates[1] also found that I[131] angiotensin was destroyed more rapidly on incubation with serum from patients with essential hypertension than with serum from normotensive patients, and this was confirmed, using a different technique, by Hickler and co-workers.[48] Recently other workers, however, assaying angiotensinase chemically, have failed to confirm a difference.[49] It appears that no difference is found when angiotensinase is determined by chemical means, whereas the difference does appear when the half life[11,48a] of angiotensin is determined on incubation with serum. The test as performed in our laboratory and in others is, however, too cumbersome for use as a routine test. Also, it is not clear whether it could differentiate renal from essential hypertension.

Meanwhile Gitlow and associates[50] also working in our laboratory found the plasma disappearance rate of infused tritiated norepinephrine to be more rapid

than normal in essential hypertension. This was obviously impractical for routine use requiring elaborate serial analyses. It did, however, along with the digital vascular NE reactivity test, suggest that the patient with essential hypertension handles infused NE differently from the normotensive subject. Uremic patients, on the other hand, when tested with this technique had disappearance rates which were slower than normal even if the uremia was caused by the nephrosclerosis of essential hypertension.[64]

At about this time several laboratories were working on the metabolites of the catecholamines.[7-68] The metanephrines, 3-methoxy-4-hydroxyphenylethylene glycol and vanillylmandelic acid could be easily assayed in the urine but these were metabolites of both epinephrine as well as norepinephrine. Within the past three years normetanephrine was separated from metanephrine by several laboratories[65,66] and in our laboratory a simple technique for doing this using high voltage electrophoresis on a paper strip was developed by Wolf and associates.[67,68] It soon became clear that metanephrine could comprise anywhere from 20 to 60 per cent of the total combined normetanephrine and metanephrine, much more in man than had been presumed from animal studies.[67,68] An attack on the metabolism of norepinephrine therefore required the isolation of a specific metabolite, namely, normetanephrine. Simple excretion studies in patients with hypertension, however, showed only trends toward a lower excretion of the metabolite but not at levels statistically significant.[69]

It was thus decided to measure apparent NE secretion rates (NESR) using the same technique described for other substances.[69] A specific amount of tritiated NE is injected intravenously and a 24 hour urine collected. This urine is subjected to high voltage electrophoresis and the specific activity of normetanephrine is measured. The secretion rate is determined by dividing the counts injected by the specific activity of NM as follows:

$$NESR = \frac{\dfrac{^{3}H\,NE\ (counts)}{^{3}H\,NM\ (counts/day)}}{NM\ (mg./day)}\ \text{or}\ \frac{^{3}H\,NE}{^{3}H\,NM} \times NM$$

This test developed by Wolf and associates[8,63,64] clearly differentiates subjects with essential hypertension from normotensive subjects and patients with renal hypertension or pheochromocytoma. The normal range is 26 to 78. The essential hypertensive cases are all below normal and range from 3 to 26 whereas the renal hypertensive cases fall into the normal range if they are not complicated by essential hypertension. Pheochromocytoma cases are all above normal. The test is relatively simple to perform, but does require high voltage electrophoresis, liquid scintillation counter, strip counting equipment, and the like, as well as tritiated NE. Its cost is therefore high.

One may argue that this test is not a true measure of secretion and that it is impossible to measure this accurately because there are different pools of NE secreted at different rates.[64] This is undoubtedly true and the apparent secretion rate as presented is only a crude lumping together of these factors. The results may also be different in essential hypertension because of a different distribution of the injected label in the various pools involved. The fact remains, however, that the results are grossly and specifically different in the essential hypertension group.

There are several other tests, thought at one time to be useful in essential hypertension, none of which is practical. They all involve sodium metabolism. One of these is the increase in renal sodium excretion on heavy solute loading.[70-47] This test, although normal in renovascular hypertension, is not, however, specific for essential hypertension and may be positive with metaraminol infusion[64] or negative on repeated measurement, etc. Another such test is measurement of retention of sodium on light solute loading in hypertension[74] and there is also no indication that this test is specific for essential hypertension. Both these tests are too complex for routine use. Another test is the demonstration of an increased sodium pool in essential hypertension after injection of Na^{22} and total body counting.[72] Previously reported differences between hypertensive and normotensive subjects, however, have not been confirmed in a more comprehensive study.[73] Additional tests are the measurement of aldosterone excretion[73,74] and

secretion.[67,73] Both these tests are positive in the accelerated phase of essential hypertension due to secondary hyperaldosteronism. They cannot, however, be used as specific tests for essential hypertension since hyperaldosteronism occurs in other conditions and does not occur very often in the so-called benign phase of essential hypertension.

We must now ask ourselves in what clinical situations any of this extensive testing may become necessary. In our opinion, they fall into four categories: (1) where primary hyperaldosteronism is suspected; (2) certain cases in which pheochromocytoma is suspected; (3) in very early hypertension when true essential hypertension must be differentiated from purely psychogenic transient hypertension due to anxiety; and (4) where mixed etiology is present or suspected as in certain cases of renovascular hypertension or parenchymatous nephritis and especially where surgical intervention such as vascular repair, nephrectomy, or transplantation may be indicated.

From a practical point of view, the major screening tests available for primary hyperaldosteronism are determination of serum sodium, potassium, carbon dioxide, and chloride and urine pH. These must be done after all diuretics have been discontinued for at least two weeks and preferably done more than once. One looks for alkalosis, hypernatremia, and particularly hypokalemia. Another test is the failure of desoxycorticosterone to suppress aldosterone excretion.[76] If any of these tests are suspicious, further testing is in order. It is at present impractical to do routine screening tests in all patients with hypertension for renin [77] and aldosterone.[67,73] The former is an elaborate costly test done in only a few laboratories in the country and the latter is also costly and difficult. It is possible that some cases of normokalemic primary aldosteronism are buried in the essential hypertensive group,[78] although these are probably few in number.

If the preliminary screening tests, however, should be suspicious, then further testing is warranted. This includes determination of venous plasma renin activity with the patient ambulant and on a low sodium [illegible] [illegible][66] and also determination of urine aldosterone[77] and if necessary the aldosterone secretion rate.[7] There is a modification of the renin test being developed that is promising and does not involve a final rat assay. It is a radioimmunologic test for angiotensin II developed by Valloton and associates[81] and modified in other laboratories.[82] The first step for renin assay remains unchanged. This involves incubation of the plasma so that angiotensin I is produced by the action of renin on its substrate, angiotensinogen. A converting enzyme in the plasma produces angiotensin II from angiotensin I. Such a test might make screening for primary hyperaldosteronism more available as well as more effective. Blood volume determination with labeled albumin and hemoglobin is also desirable as are sodium and potassium balance studies in the hospital.[83] If these tests and the aldosterone tests are positive and the renin test result low or negative, exploratory operation is justified.

There are, however, other flies in this ointment. Only about two thirds of the patients operated upon for primary hyperaldosteronism have thus far been cured of their hypertension. One fourth falls into an improved category and there is a small percentage of failures. We do not know how such patients respond to antihypertensive drugs and whether any of the cases have mixed forms of hypertension, an incidence which would not be unlikely. Also the blood pressure falls, when it does after operation, over a period of eight months or more, a circumstance difficult to understand. There are also rare cases of congenital primary hyperaldosteronism with only adrenal hyperplasia. These cases must be differentiated from patients with adenomas by giving them a course of dexamethasone therapy. In the congenital group this causes the hypertension to decrease and other manifestations of hyperaldosteronism to disappear. In addition, some cases of secondary hyperaldosteronism may have decreased plasma renin activity which could be confusing and result in unnecessary operation.[84]

In certain cases where pheochromocytoma is suspected, more elaborate testing may also be necessary. We have learned in earlier years from bitter experience consisting of unnecessary operations, that if

there is a conflict [?] the tests are to be trusted rather than clinical evaluation. If the urine CM test for pheochromocytoma is strongly positive there is no serious problem except for confirmation of the finding before operation. It is in the occasional cases that fall into the borderline zone where we have the most difficulty. These consist of cases of cystic tumors with low catecholamine outputs[?,?] and cases of essential hypertension in which serious associated illness or coma may have increased the urinary output of the catecholamines.[?,?] It is in such cases that repeated testing for urinary metabolites becomes necessary and the apparent NE secretion rate test may be helpful. We have abandoned pharmacologic testing for pheochromocytomas and advise against pyelography or air insufflation techniques because of their danger. Chest x-ray is always indicated to identify the occasional tumor in the thorax and renal tomography can still be used. Since 20 per cent of the cases are bilateral, however, the transabdominal surgical approach often makes the latter procedure superfluous.

Another source of confusion arises when we attempt to differentiate between anxiety states producing hypertension and true early essential hypertension.[?] This problem occurs more often in the younger than in the older age group. Furthermore, the two conditions are quite common and may coexist. A family history of hypertension is helpful but not diagnostic. The diastolic pressure in either condition may or may not be above 90. The cold pressor test is of little help in this situation and may be positive in both conditions. No experience with the angiotensin infusion test in this regard has been reported. The digital vascular reactivity test, however, with either NE or angiotensin is always positive if there is underlying essential hypertension[?] and negative if there is pure anxiety. This also holds for the apparent NE secretion rate test.[?] When these two tests are negative, therefore, one can be reasonably sure that there is no essential hypertension and that the blood pressure elevations observed are due to anxiety only. A further test is to ask the patient to record home blood pressures. In our experience the correlation between normal home blood pressure and negative tests and vice versa between elevated home blood pressure and positive tests has been excellent.[?] It is not feasible, however, to obtain home blood pressures on all patients so that not every patient can be tested further in this way. Moreover, these tests only identify essential hypertension and an anxiety state still remains a clinical determination. Also, the final validation of such testing must await long-term observation of patients to see whether any of those declared to be anxiety only ever develop full-blown essential hypertension.

The most difficult problem of all, however, is brought about by the frequent occurrence of cases of mixed etiology.[?,?] That this is so should not be surprising. Essential hypertension is a common disease and it is estimated that at least one out of every ten persons will eventually develop it.[?,?] What is more, it is now evident that chronic pyelonephritis occurs more frequently in the patient with underlying essential hypertension.[?-?] Whether this is true of other types of parenchymatous renal disease is conjectural but fortuitous association could still be quite common. Nephrosclerosis is, of course, produced by essential hypertension and complicates it in the accelerated phase of the disease.[?,?] The association of renovascular hypertension with essential hypertension has already been discussed.

Only if a surgical procedure such as renovascular repair, transplantation, or nephrectomy is contemplated need the testing be elaborate. The renal function tests have already been discussed, but it should be emphasized that tests for essential hypertension are also necessary. In our hands, the most valuable of these are the digital vascular reactivity test and the apparent NE secretion rate test. If these tests are positive for essential hypertension, they may eventually serve to influence the decision as to whether to subject certain patients to the operation contemplated. This, of course, would have to await further experience with these tests and correlation of the results with the end results of the operative procedure. Percutaneous renal biopsy is only occasionally

necessary for the evaluation of renovascular hypertension but may be needed when transplantation is contemplated

One aspect of this problem has been brought home to us over the years and that is the fallibility of clinical evaluation in this confusing field Even pathological evaluation often has been found to be equally fallible. Numerous examples of past error in interpretation can be cited in this regard One need only mention myocardial infarction correctly interpreted pathologically only after clinical clarification[96, 97] and the difficulty in interpreting end-stage renal disease[98] the conflicting interpretation of renal biopsy as against autopsy material[99-100] the emergence of new renal diseases such as membraneous glomerulonephritis[101] and lupus nephritis[102] despite the fact that the diseases themselves are by no means new Recently nephrosclerosis has been much more frequently interpreted correctly by pathologists as against previous interpretations of similar pathological pictures as primary parenchymatous renal disease such as chronic glomerulonephritis, etc. Clinicians, however and pathologists also do move with the times and do apply newer knowledge to both clinical and pathological evaluation in their fields.

The lesson to be learned from all this is if the test is a good one trust the result[1] If it does not coincide with the clinical picture or pathological evaluation perhaps these are wrong or maybe the patient has more than one cause for his hypertension. Moreover prehypertension cases may be expected to have abnormal results on testing[103] and these may fortuitously dilute the normal group so that some overlapping may be expected in many of these tests. In this field as in others, proper over all evaluation will only be improved with the knowledge accumulated by objective testing and continuing research.

Summary

1 In addition to routine clinical "work up" including history physical examination ECG chest x ray blood count urine analysis, colony count, and culture erythrocyte sedimentation rate blood urea nitrogen, fasting blood sugar serum cholesterol uric acid calcium phosphorus and electrolytes, every hypertensive patient should also have a rapid-sequence intravenous pyelogram and a catecholamine metabolite test.

2 In Cushing's syndrome urinary and/or blood assay for 17 hydroxycorticoids and 17-ketosteroids will be needed

3 In primary hyperaldosteronism tests for excretion and secretion of aldosterone as well as tests for serum renin are important. A trial of dexamethasone therapy is indicated to exclude "congenital hyperaldosteronism

4 In pheochromocytoma, the catecholamine metabolite test must be confirmed by the Euano test for metanephrines and by a test for vanillylmandelic acid In doubtful cases the apparent NE secretion rate test may be useful

5 In renovascular hypertension the tests needed are the rapid-sequence intravenous pyelogram and aortogram for purposes of diagnosis If operation is being considered a Howard or Stamey test is in order together with renal vein renin assay Other tests may be needed here in special situations such as the radioactive renogram aldosterone assays, etc.

6 In all cases where operation is contemplated including cases in which renal transplantation may be of value tests for essential hypertension should also be carried out. In our hands, the two most useful tests of this kind are the norepinephrine or angiotensin digital vascular reactivity test and the apparent norepinephrine secretion rate test.

7 The latter two tests are also useful in differentiating true early essential hypertension from anxiety states producing transient hypertension

REFERENCES

1 Hamolsky M W Stein, M and Freedberg A. S. The thyroid hormone-plasma protein complex in man II New in vitro method for study of uptake of labelled hormonal components by human erythrocytes, J Clin Endocrinol 17:33 1957

2. Wolf R L Mendlowitz, M Roboz, J and Gitlow S. E. Simultaneous urinary assays for the combined metanephrines and 3-methoxy-4-hydroxyphenylglycol in patients with pheo-

chromocytoma and primary hypertension, New England J. Med. 272:1459, 1965.
3. Meilman, E., Azulay, A., and Butterly, J. M.: Clinical diagnosis of renal artery constriction, Circulation 20:740, 1959.
4. Pisano, J. J.: Simple analysis for normetanephrine and metanephrine in urine, Clin. chim. acta 5:406, 1960.
5. Armstrong, M. D., McMillan, A., and Shaw, K. N. F.: 3-Methoxy-4-hydroxy-D-mandelic acid, urinary metabolite of norepinephrine, Biochim. et biophys. acta 25:422, 1957.
6. Paschkis, K. E., Rakoff, A. E., Cantarow, A., and Rupp, J. J.: Clinical endocrinology, Ed. 3, New York, 1967, Hoeber Medical Division, Harper & Row, Publishers, Inc., p. 303.
7. Deyton, W. H., Martin, J. F., Boyce, W. H., and Glenn, J. F.: Differential renal function evaluation by minute sequence pyelography, J. Urol. 90:611, 1963.
8. Amplatz, K.: Two radiographic tests for assessment of renovascular hypertension, Radiology 79:807, 1962.
9. Peart, W. S.: Hypertension and the kidney. I. Clinical, pathological, and functional disorders, especially in man, Brit. M. J. 2:1353, 1959.
10. Glenn, J. F., and Anderson, E. E.: Reversible renovascular hypertension, Ann. Rev. Med. 18:219, 1967.
11. Seldinger, S. I.: Catheter replacement of the needle in percutaneous arteriography: new technique, Acta radiol. 39:368, 1953.
12. Amplatz, K.: Assessment of curable renovascular hypertension by nephrectomy in four patients with unilateral renal vascular disease, Radiology 83:816, 1964.
13. DeBakey, M. E., Morris, G. C., Jr., Morgen, R. O., Crawford, E. S., and Cooley, D. A.: Lesions of the renal artery, Am. J. Surg. 107:84, 1964.
14. Howard, J. E., Berthrong, M., Sloan, R. D., and Yendt, E. R.: Relief of malignant hypertension by nephrectomy in four patients with unilateral renal vascular disease, Tr. A. Am. Physicians 66:164, 1953.
15. Stamey, T. A., Nudelman, I. J., Good, P. H., Schwentker, F. N., and Hendricks, F.: Functional characteristics of renovascular hypertension, Medicine 40:347, 1961.
16. McPhaul, J. J., McIntosh, D. A., Williams, L. F., Grittl, F. J., Malette, W. G., and Grollman, A.: Pressor activity of renal venous blood in hypertension, Ann. Int. Med. 61:847, 1964.
17. Winter, C. C.: Radioisotope renography, Baltimore, 1963, The Williams & Wilkins Company.
18. Kiser, W. S., Tanenbaum, H. L., and Holland, J. M.: The phonorenogram: transureteral phonocatheter recording of the renal artery pulse in the diagnosis of renal vascular disease, J. Urol. 92:391, 1964.
19. Kioschos, J. M., Kirkendall, W. M., Valenca, M. R., and Fitz, A. E.: Unilateral renal hemodynamics and characteristics of dye-dilution curves in patients with essential hypertension and renal disease, Circulation 35:229, 1967.
20. Gunnels, J. C., Jr., Grim, C. E., Robinson, R. R., and Wildermann, N. M.: Plasma renin activity in healthy subjects and patients with hypertension, Arch. Int. Med. 119:232, 1967.
21. Crocker, D. W., Newton, R. A., Mahoney, E. M., and Harrison, J. H.: Hypertension due to primary renal ischemia: a correlation of juxtaglomerular cell counts with clinicopathologic findings in 25 cases, Tr. Am. A. Genitourin. Surg. 53:96, 1962.
22. Hines, E. A., Jr., and Brown, G. E.: A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state, Ann. Int. Med. 7:209, 1933.
23. Wolff, H. H.: The mechanism and significance of the cold pressor response, Quart. J. Med. 20:261, 1951.
24. Tuckman, J., Kakavintos, N., and Finnerty, F. A., Jr.: Effects of the cold pressor test on cardiac output and peripheral resistance, Circulation 28:818, 1963.
25. Kaplan, N. M., and Silah, J. G.: The angiotensin infusion test: new approach to the differential diagnosis of renovascular hypertension, New England J. Med. 271:536, 1964.
26. Mendlowitz, M., Naftchi, N. E., Wolf, R. L., and Gitlow, S. E.: Vascular reactivity in the patient with essential hypertension and hypertension of renal origin, Am. J. Cardiol. 9:680, 1962.
27. Mendlowitz, M., Naftchi, N. E., Gitlow, S. E., and Wolf, R. L.: Vascular responsiveness in hypertensive and hypotensive states, Geriatrics 20:797, 1965.
28. Mendlowitz, M., and Naftchi, N.: Work of digital vasoconstriction produced by infused norepinephrine in primary hypertension, J. Appl. Physiol. 13:247, 1958.
29. Wolf, R. L., Mendlowitz, M., and Roboz, J.: A new test for primary hypertension: the apparent norepinephrine secretion rate in normotensive and hypertensive man, J. Clin. Invest. 46:1134, 1967.
30. Wollheim, E.: Die essentielle Hypertonie als nosologische Einheit und ihre Differentialdiagnose, Verhandl. Deutsch. Gesellsch. Kreislaufforsch. 28:39, 1962.
31. Smythe, C. M., Rivers, C. F., and Rosemond, R. M.: A comparison of the incidence of bacteriuria among hypertensives and matched controls, Arch. Int. Med. 105:899, 1960.
32. Shapiro, A. P.: Susceptibility of rats with DCA hypertension to experimental pyelonephritis and aggravation of DCA hypertension by renal infection, J. Lab. & Clin. Med. 55:715, 1960.
33. Klemperer, P., and Otani, S.: Malignant nephrosclerosis (Fahr), Arch. Path. 11:60, 1931.
34. Brest, A. N., and Moyer, J. H.: The significance and incidence of renal atherosclerosis in hypertension, in Brest, A. N., and Moyer, J. H., editors: Hypertension: recent advances, Philadelphia, 1961, Lea & Febiger, p. 181.
35. Stamey, T. A.: Renovascular hypertension, Baltimore, 1963, The Williams & Wilkins Company, p. 134.
36. Poutasse, E. F.: Surgical treatment of renal hypertension, Am. J. Surg. 107:97, 1964.

37 Poutasse, E. F and Dustan, H. P Surgical treatment of renal hypertension, *I* Moyer J H., editor: Hypertension, Philadelphia and London, 1959 W B Saunders Company p. 630.
38. Mendlowitz, M Vascular reactivity in essential and renal hypertension in man, Am. Heart J 73 121 1967
39 Fitz, A. E., V lenca, M and Kirkendall, W M Angiotensin infusion test (AIT) in normal and hypertensive subjects, Clin. Res 13:206, 1965
40. Mortson, S E., Perez Stable, E., and Shapiro, A. P Diagnostic and physiological implications of the angiotensin infusion test, Circulation 32:156, 1965 (Suppl. II).
41 Breckenridge A. Angiotensin-inf sion test, Lancet 2:209 1965.
42 Nicotero, J A., Mortson, S E., Perez-Stable, E., Turrian, H. E., and Shapiro, A P Diagnostic and physiologic implications of the angiotensin infusion test, New England J Med. 274:1464, 1966.
43 Mendlowitz, M The digital circulation, New York, 1954 Grune & Stratton, Inc.
44 Mendlowitz, M Torosdag S. M and Sharney L.: The force and ork of digital arteriolar vasoconstriction in hypertension, J Appl. Physiol. 10:436, 1957
45. Mendlowitz, M Naftchi, N Wolf R. L., and Gitlow S. E. The effect of aldosterone on electrolytes and on digital vascular reactivity t *l*-norepinephrine in normotensive, hypertensive, and hypotensive subjects, Am. Heart J 65:93, 1963.
46. Mendlowitz, M Naftchi, N Weinreb, H. L., and Gitlow S. E. The effect of prednisone and prednisolone on reactivity of the digital blood vessels t *l*-norepinephrine in normotensive and hypertensive subjects, J Appl. Physiol. 16:89 1961
47 Mendlowitz, M Gitlow S., and Naftchi, N Work of digital vasoconstriction produced by infused norepinephrine in Cushing syndrome, J Appl. Physiol. 13:252, 1958.
48 Wolf R. L Mendlowitz, M Gitlow S E., and Naftchi, N E Angiotensin II I[131] metabolism in normotensive and hypertensive human subjects, Circulation 23 754 1961
49 Wolf R L., Mendlowitz, M Pick, J Gitlow S E and Naftchi, N I itro degradation of I[131]-labeled angiotensin II by normotensive and hypertensive human serum, Proc. Soc Exper Biol. & Med. 109:308, 1962.
50 Hickler R B Lauler D P and Thorn, G. W Plasma ngiotensinase activity in patients ith hypertension and edema, J Clin Invest. 42:635 1963
51 Itskovitz, H D Dudrich, S. J Dyrda, I and Murphy J J Plasma angiotensinase activity in hypertensive patients, Arch I t. Med. 119:241 1967
52 Lubash, G. D Angiotensinase and renin activities in hypertension, Clin. Res. 15:363, 1967
52a. Beretta, R Fantini, F Ciconali, M and Marini, I Determinazione dell' ttivita angiotensinasica del plasma di soggetti normotesi ipertesi, Att. Acad. Med. Lombard 21 1 1966
53 Gitlow S. E., Mendlowitz, M Kruk Wilk, E Wilk, S., Wolf, R. L., and Naftchi, N E. Plasma dl-β-H[3]-norepinephrine clearance in normal subjects and in patients w th essential hypertension, J Clin. I vest. 43:2009 1964
54 Gitlow S. E. Unpublished observations.
55 Sjoerdsma, A., Leeper L. C., Terry L. L., and Udenfriend, S. Studies on biogenesis and metabolism of norepinephrine in patients with pheochromocytoma, J Clin. I vest. 38:31 1959
56 Axelrod, J Kopin, I J and Mann, J D 3-Methoxy-4-hydroxyphenylglycol sulfate new metabolite of epinephrine and norepinephrine, Biochem. et biophy acta 36:576, 1959
57 Armstrong M D nd McMillan, A Identification of major urinary metabolite of norepinephrine Fed. Proc. 16 146, 1957
58. von Studnitz, W and Hanson, A. Determination of 3-methoxy-4-hydroxy-mandelic acid in urine by high-voltage paper electrophoresis, Scandinav J Cli & Lab. Invest. 11 101 1959
59 von Studnitz, W Separation nd determination of metadrenaline and meta-noradrenaline by high-voltage paper electrophoresis, Clin. chim. acta 5:447 1960.
60. Yoshinaga, K. Itoh, C Ishida, N Sato, T and Wada, Y Quantitative determination of metadrenaline and normetadrenaline in normal human urine, N ture (London) 191:599 1961
61 Wolf R. L., and Roboz, J Urinary normetanephrine and metanephrine excretion separately assayed, following the oral administration of guanethidine, Fed. Proc. 25:625 1966
62 Wolf R L Mendlowitz, M Roboz, J Naftchi, N E and Gitlow S. E Urinary normetanephrine and metanephrine excretion, separately assayed, in normotensive, hypertensive and pheochromocytoma patients, J Clin Invest 45:1088, 1966.
63. Ulick, S., Laragh, J H nd Lieberman, S Isola ion of urinary metabolite of ldosterone and its use t measure the rate of secretion of ldosterone by the adrenal cortex of ma T A Am Ph icians 1:225 1958
64 Wolf R L Mendlowitz, M Roboz, J G tlow S., and Naf ch N Diurnal nd nocturnal urinary normetanephrine and metanephrine, separatel assa ed in normotensive nd hypertensiv subject C rc lation 34:241 1966
64a. Wolf R L Mendlowitz M and Roboz, J Distribu ion k etic apparent secretion rat nd t rnover of orepinephrine in man, Circulat n Suppl II 36:273 1967 (Abstr)
65 Green D M W dell, M D Wald, M H and Learned, B The relation of water nd sod m excre n blood pressure in human subjec Circulation 6 191 1952
66 Cottier P T Renal hemodynamics, ter and lectrol excretion in essential hypertension. Bock, K D and Cottier P T editors Essential hypertension Ciba Foundation I ernat. Symposium, Berlin, 1960, Springer Verlag p 66.

67. Baldwin, D. S., Biggs, H. W., Goldring, W., Hulet, W. H., and Chasis, H.: Exaggerated natriuresis in essential hypertension, Am. J. Med. 24:893, 1958.
67a. Lowe, H. M., and Singelyn, M.: Salt loading in hypertension due to renal artery stenosis, Circulation 32:888, 1965.
68. Elsinger, R. P.: Augmented natriuretic response to infusion of saline in dogs rendered acutely hypertensive with metaraminol, Proc. Soc. Exper. Biol. & Med. 122:804, 1966.
69. Weiner, A., and Green, J. J.: Effect of simple deconditioning procedure on the diuretic and natriuretic response of hypertensive patient to a hypertonic salt load, Circulation 35:260, 1967.
70. Baldwin, D. S., Gombos, F. A., and Chasis, H.: Urinary concentrating mechanism in essential hypertension, Am. J. Med. 38:864, 1965.
71. Dahl, L. K., Smilay, M. G., Silver, L., and Spraragen, S. C.: Prolonged biological half life of sodium 22 in patients with essential hypertension, Nature 192:267, 1961.
71. Dahl, L. K., Lax, L. C., Yang, C. H., Schackow, E., and Knudsen, K. D.: Failure to confirm prolongation of the biological half life of of sodium 22 in hypertensive patients, Circulation Res. 19:750, 1966.
72. Genest, J., Lemieux, G., Davignon, A., Koiw, F., Nowaczynski, W., and Steyermark, P.: Human arterial hypertension: a state of mild chronic hyperaldosteronism, Science 123:503, 1956.
73. Conn, J. W.: Primary aldosteronism, a new clinical syndrome, J. Lab. & Clin. Med. 45:3, 1955.
74. Deming, Q. B., and Luetscher, J. A., J.: Bioassay of desoxycorticosterone-like material in urine, Proc. Soc. Exper. Biol. & Med. 73:171, 1950.
75. Laragh, J. H., Ulick, S., Januszewicz, V., Deming, Q. B., Kelly, W. G., and Lieberman, S.: Aldosterone secretion and primary and malignant hypertension, J. Clin. Invest. 39:1091, 1960.
75a. Biglieri, E. G., Slaton, P. E., Kronfeld, S. J., and Schambelan, M.: Diagnosis of an aldosterone-producing adenoma in primary aldosteronism, J.A.M.A. 201:510, 1967.
76. Helmer, O. M., and Judson, W. E.: The quantitative determination of renin in the plasma of patients with arterial hypertension, Circulation 27:1050, 1963.
77. Genest, J., Boucher, R., DeChamplain, J., Veyrat, R., Chretién, M., Biron, P., Tremblay, G., and Roy, P.: Studies on the renin-angiotensin system in hypertensive patients, Canad. M. A. J. 90:263, 1964.
78. Conn, J. W., Rovner, D. R., Cohen, E. L., and Nesbit, R. M.: Normokalemic primary aldosteronism, J.A.M.A. 195:21, 1966.
79. Conn, J. W.: The evolution of primary aldosteronism, 1954-1967, Harvey Lectures, 1967 (in press).
80. Conn, J. W.: Plasma renin activity in primary aldosteronism, J.A.M.A. 190:222, 1964.
81. Valloton, M., Page, L., Haber, E., and Lazy, S.: Determination of angiotensin II and renin activity in human plasma by radioimmunoassay, J. Clin. Invest. 46:1126, 1967.
82. Wolf, R. L.: Unpublished data.
83. Biglieri, E. G., and Forsham, P. H.: Studies on the expanded extracellular fluid and the response to stimuli in primary aldosteronism, Am. J. Med. 30:564, 1961.
84. Laragh, J. H., Ledingham, J. G. G., and Sommers, S. C.: Secondary aldosteronism and reduced plasma renin in hypertensive disease, T. A. Am. Physicians (in press).
85. Gitlow, S. E., Mendlowitz, M., and Wolf, R. L.: The diagnosis of pheochromocytoma, Mendlowitz, M., editor: Hypertension, New York and London, 1961, Grune & Stratton, Inc., p. 63.
86. Crout, J. R., Pisano, J. J., and Sjoerdsma, A.: Urinary excretion of catecholamines and their metabolites in pheochromocytoma, Am. Heart J. 61:375, 1961.
87. Gitlow, S. E., Mendlowitz, M., Kruk, E., and Khassis, S.: The diagnosis of pheochromocytoma by assay of catecholamine metabolites, Proc. council for high blood pressure research, Circulation Res. 9:715, 1961.
88. Pickering, G. W.: High blood pressure, New York and London, 1955, Grune & Stratton, Inc., p. 211.
89. Mendlowitz, M., Naftchi, N. E., Gitlow, S. E., and Wolf, R. L.: Vascular responsiveness in hypertensive and hypotensive states, Geriatrics 20:797, 1965.
90. Mendlowitz, M.: Unpublished data.
91. Page, I. H.: The mosaic theory of hypertension, Bock, K. D., and Cottier, P. T., editors: Essential hypertension, CIBA Foundation Internat. Symposium, Berlin, 1960, Springer Verlag, p. 1.
92. Mendlowitz, M., Gitlow, S. E., Wolf, R. L., and Tuckman, J.: The metabolism of hypertension, Am. Heart J. 70:677, 1965.
93. Pickering, G. W.: High blood pressure, New York and London, 1955, Grune and Stratton, Inc., p. 177.
94. Stamler, J., Stamler, R., and Pullman, T. N.: The epidemiology of hypertension, New York and London, 1967, Grune and Stratton, Inc.
95. Imbriglia, J. E.: Pathology of hypertension as a generalized vascular disease, Moyer, J. H., editor: Hypertension, Philadelphia and London, 1959, W. B. Saunders Company, p. 1.
96. Herrick, J. B.: Clinical features of sudden obstruction of the coronary arteries, J. A. M. A. 59:2015, 1912.
97. Sprague, H.: Coronary heart disease: coronary occlusion and myocardial infarction, Levy, R. L., editor: Disorders of the heart and circulation, New York, 1951, T. Nelson & Sons, p. 437.
98. Churg, J., Strauss, L., and Paronetto, F.: Some aspects of the pathology of hypertension, in Mendlowitz, M., editor: Hypertension, New York and London, 1961, Grune & Stratton, Inc., p. 13.
99. Kark, R. M.: Renal biopsy and prognosis, Ann. Rev. Med. 18:269, 1967.

100. Iverson, P. and Brun, C. Aspiration biopsy of the kidney. Am. J. Med. 11:324, 1951.

101. Kark, R. M., Pirani, C. L., Pollak, V. E., Muehrcke, R. C., and Blainey, J. D. The nephrotic syndrome in adults, common disorder with many causes, Ann. Int. Med. 49:751, 1958.

102. Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollak, V. E.: Lupus nephritis: clinical and pathologic study based on renal biopsies, Medicine 36:1, 1957.

103. Doyle, A. E., and Fraser, J. R. E. Essential hypertension and inheritance of vascular reactivity. Lancet 2:509, 1961.

Appraisal and reappraisal of cardiac therapy

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Surgical treatment of valvular heart disease

Part III. Surgical repair of the stenotic mitral valve

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Before the development of surgical techniques for the correction of mitral stenosis, the disease inexorably led to death, usually in the sixth decade of life. The slow, progressive decline in cardiac performance characteristic of mitral stenosis was sometimes accelerated by bacterial endocarditis or arterial embolism. Since 1948, when the first acceptable surgical manipulations of the valve were performed, the natural history of mitral stenosis has been radically altered. Incapacitating symptoms have been relieved and the longevity of surgical survivors increased. Despite an incomplete understanding of mitral valve pathology and function, and the use of techniques now considered obsolete, there were lasting beneficial results in almost half the operated cases.

The problem of early and late deterioration of surgically treated cases had not been foreseen in the early years of closed mitral surgery, although it was apparent to most workers that relief of mitral stenosis was not being achieved with regularity. Thick fibrous commissures, calcified leaflets, and subvalvular stenosis due to fusion, thickening and shortening of chordae tendineae defied the best efforts of surgeons working in the closed heart. Clinical signs of mitral stenosis often persisted after operation although some patients felt improved because of elation upon survival from surgery or from intensified medical care. Late clinical deterioration was observed in some patients who had good anatomical and physiological results at operation.

Knowledge of the surgical anatomy of the mitral valve, appreciation of the requirements of adequate commissurotomy, improved closed techniques for enlarging the mitral orifice, and the application of safe direct vision open techniques for the relief of mitral stenosis have enhanced the potential for consistent and prolonged surgical relief of mitral stenosis.

Selection of patients for mitral valve surgery. Surgical relief of mitral stenosis is advised when progressive symptoms of cardiac insufficiency are associated with evidence of physiologically significant mitral valve obstruction. The latter can be demonstrated on physical examination, by electrocardiography, by radiographic detection of enlargement of the left atrial and right

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ventricular chambers, or by sophisticated laboratory documentation of hemodynamic abnormality.

Surgery is not warranted for asymptomatic mitral stenosis. When progressive dyspnea, fatigue or congestive heart failure are observed and there is a consequent withdrawal by the patient from appropriate physical activities, surgery is advised. The level of cardiac performance required for any individual is variable, and consequently surgery is indicated by individual circumstances rather than by an arbitrary standard of performance. Arterial embolism is a compelling indication for surgery although the associated clinical disability may be mild. The incidence of recurring emboli is reduced by adequate mitral commissurotomy.

It is possible to predict the condition of the valve with accuracy in advance of the operative procedure. The type of reparative procedure is usually predictable in advance of surgery, especially with reference to the potential need for valve replacement. Predictions are based upon age, sex, purity of the stenosis, basic heart rhythm, heart sounds, and radiographic evidence of valvular calcification. The young female with pure non-calcific stenosis, a good first mitral sound and opening snap, and regular sinus rhythm is likely to have a pliable valve which can be corrected by simple commissurotomy.

Surgery may be deferred with justification in the minimally incapacitated patient who if brought to surgery would require mitral valve replacement. With the passage of time such patients will be operated upon earlier in the course of their disease as improved prosthetic mitral valves become available.

Physiological evaluation. There are neither absolute hemodynamic indications nor contraindications to mitral valve repair. Most patients with mitral stenosis do not require cardiac catheterization prior to surgery. On rare occasions, it may be desirable to confirm the presence of mitral obstruction by laboratory methods when clinical evaluation is uncertain. When aortic and tricuspid valve lesions are suspected clinically, radiologic and hemodynamic methods can help the surgeon plan an operative procedure designed to correct the significant organic lesions. The research value of serial hemodynamic studies is also recognized.

Objectives of surgery. The surgeon's task is to eliminate mitral valvular and subvalvular stenosis, remove intracardiac thrombus, avoid thrombotic and calcific emboli, and avoid or repair significant mitral insufficiency. The surgeon must fulfill these objectives with safety and regularity. Failure to obtain a good clinical result after mitral surgery implies that the hemodynamic result at the mitral orifice is unsatisfactory. While myocardial disease, multivalvular involvement, or progressive destruction of the mital valve by disease may compromise a surgical result, a major cause of disappointment is the failure to achieve the stated objectives of surgery.

Surgical technique. Finger fracture of the stenosed mitral valve commissures was introduced nearly 20 years ago. Various aids to the surgeon's finger were devised to assist in the accuracy or forcefulness of the manipulation. The ungloved index finger permitted more accurate palpation of the valve, and the exposed fingernail was used as a dissector. Fingertips were enlarged with tape to increase the diameter of the dilating wedge. Thimbles and knives were carried blindly into the heart to cut resistant commissures. In 1959, Logan and Turner[3] introduced the transventricular dilator, which has since been widely used by surgeons in the United States. This instrument is introduced *through the apex of the* left ventricle and guided into position by a finger in the left atrial chamber. The strictured valve is forcibly divulsed, usually lines of fusion, with the initial opening at the least resistant commissure. Although forcible dilatation can injure valve leaflets and chordae tendineae, the over all superiority of this method over transatrial methods has been generally accepted.

There have been relatively few proponents of elective open heart surgery for the routine enlargement of the mitral orifice. Lillehei and associates were the first to perform reparative surgery under direct vision in 1956. Later, Nicholas and associates[3] and Kay and colleagues[4] suggested the superiority of this method. Our recent experience with elective open heart surgery for mitral

stenosis confirms the judgments of these earlier reports. The quality of repair possible on the mitral valve under open conditions has proved superior to that possible under closed conditions and the objectives of surgery are more frequently fulfilled

Open mitral commissurotomy with cardiopulmonary by pass permits the surgeon to perform an unhurried visually guided controlled complete mobilization of all valve components Atrial thrombus is removed when encountered and minor degrees of mitral insufficiency are easily corrected

Results

The immediate hemodynamic effects of repair of the mitral valve is the abolition of the diastolic pressure gradient between the left atrium and the left ventricle. Pulmonary artery pressure falls slightly There is neither significant improvement in cardiac output at surgery nor immediately afterward except for the temporary effect achieved by deliberate expansion of blood volume or by the use of inotropic agents Continuation of the low cardiac output into the postoperative period is probably related to impaired function of the left ventricle as is indicated by immediate postoperative hemodynamic studies.

Operative death from closed mitral procedures is 3 4 to 8 5 per cent in some large series that have been reported An earlier report on elective open repair indicated a mortality rate of 6 5 per cent. Our experience with elective open heart mitral valve repair yielded an operative mortality rate of 1 9 per cent in a consecutive series of 103 patients.[4] One patient succumbed at 35 days from causes unrelated to surgery for a total hospital mortality rate of 2 9 per cent. Complications following open heart surgery were similar to those encountered after closed surgery but the incidence of intraoperative arterial emboli was reduced greatly by the ability to control atrial thrombus when encountered

Sustained clinical improvement following surgery is noted in approximately 40 to 75 per cent of patients submitted to operation by closed techniques Long term follow up on patients operated upon by open techniques is not yet available. Superior long term results may be expected from open techniques of mitral repair if sustained improvement is related to the completeness and accuracy of the surgery on the valve.

Summary and conclusions

Nearly 20 years of experience with surgical repair of the stenotic mitral valve have demonstrated that it is of value in improving cardiac function and in increasing longevity Though at times the benefits are not permanent many unsatisfactory results can be attributed to incomplete relief of all the obstructing elements of the mitral valve Improved techniques in closed surgical procedures have yielded acceptable clinical results. Safe cardiopulmonary by pass permits accurate direct vision repair of the valve under ideal surgical conditions and it is reasonable to anticipate that a better operation will provide more enduring palliation and greater longevity Our present experience indicates an operative mortality rate of 1 9 per cent for the open operation The discovery of a perfect mitral prosthesis, however would make all conservative operations on the valve obsolete

Editors Note

Dr Robinson presents a convincing case for open repair in all patients with mitral stenosis. Next month the opposing view will be upheld by Dr George Reed In both reports surgical death has been exceedingly low It should be noted that these patients all had mitral valvotomy Surgical morbidity and death in patients requiring prosthetic replacement (after an intraoperative decision) has invariably been higher

REFERENCES

1 Ellis, L B and Harken D E. Closed valvuloplasty for mitral stenosis, New England J Med. 270:643 1964
2. Bakoulas, G and Millard K. Mitral valvotomy and embolism Thorax 21:43, 1966.
3. Nichols, H. T Blanco, G Morse D P Adam, A and Baltaza N Open mitral commissurotomy J.A.M A 182:268, 1962
4. Kay E. B Rodriguez P Haghighi, D Suzuki, A and Zimmerman, H A.: Mitral stenosis Comparative analysis of postopera

tive results following the closed and open operative approach, Am. J. Cardiol. 14:139, 1964.

5. Austen, W. G., Corning, H. B., Moran, J. M., Sanders, C. A., and Scannell, J. G.: Cardiac hemodynamics immediately following mitral valve surgery, J. Thoracic & Cardiovas. Surg. 51:468, 1966.
6. Robinson, G., and Attai, L. A.: Presented at the Fourth Annual Meeting, Society of Thoracic Surgeons, New Orleans, La., Jan. 31, 1968.
7. Logan, A., and Turner, R.: Surgical treatment of mitral stenosis with particular reference to the transventricular approach with a mechanical dilator, Lancet 2:874, 1959.
8. Lillehei, C. W., Gott, V. L., De Wall, R. A., and Varco, R. L.: The surgical treatment of stenotic or regurgitant lesions of the mitral and aortic valves by direct vision utilizing a pump oxygenator, J. Thoracic Surg. 35:154, 1958.

Annotations

Blood pressure and ageing

Scientific controversy often stimulates research and such has been the case with the much publicised argument between Platt and Pickering regarding the nature of essential hypertension. Those like Platt, who believe that people with essential hypertension suffer from a discrete inherited disorder manifested in middle age but *determined at* conception, have been challenged on the grounds that all types of evidence suggest that blood pressure is a graded characteristic whose effects depend on the level attained. Pickering and his followers, who consider that environmental and age influences predominate, with relatively minor contribution coming from polygenic inheritance, are unwilling to attribute such a common disorder to the effects of a *single pair of genes.*

The controversy is more than an academic one, although everyone would agree that decisions regarding therapy which are made on other grounds are unaffected by it. As yet, there is no conclusive evidence supporting or refuting either view but it seems possible that the findings of some of the long term population studies now in progress may produce a more accurate description of the natural *history of unexplained hypertension* and thereby account for and perhaps resolve, the conflicting views.

A recent analysis of blood pressure measurements obtained in two longitudinal epidemiological surveys in Wales seems to go some way toward this end. Representative samples of the general population of a mining valley and an agricultural area were followed since 1954 and 1956 respectively *and the factors influencing the change in blood* pressure in the 8 and 10 year intervals to 1964 are being examined.

When considering changes in any measurement which is subject to rapid fluctuation, a difficulty arises if the difference between measurements is related to the initial measurement, as these are not statistically independent of each other. It is clear that those with artificially or atypically high or low *measurements at the* original examination would, upon remeasurement, tend to reveal their more normal values. *To overcome* this difficulty the changes in blood pressures were related to the average rather than to the initial readings; the technique of multiple regression analysis was then used to allow the simultaneous examination of the relative contributions of age and mean blood pressure in predicting changes of pressure. The results were somewhat *surprising.*

Within ten year age groups, almost all the mean-pressure regression coefficients were positive, many highly significantly so, whereas rather more than half of the age coefficients were negative; in only one age group was there a significantly positive age coefficient in the analyses for both sexes, populations, and systolic and diastolic pressure changes. Having found within ten year age groups so little evidence for an effect of age in determining change of pressure, the data *for all adults* were pooled and the analysis was repeated.

The mean-pressure regression coefficients for both systolic and diastolic pressure, in each sex and population were then all positive and statistically significant (7 of the 8 at least at the 0.1 per cent level); the age coefficients were not significant with one exception—that for change of diastolic pressure in one of the female populations where the coefficient was significant at the 5 per cent level but was negative. Thus in these Welsh populations the increases in blood pressure during intervals of 8 and 10 years were found to be highly significantly related to the pressure attained but only indirectly related to age.

It is generally accepted that within the malignant phase of hypertension, the pressure itself *determines* its accelerated rate of increase. One possible explanation for these epidemiological findings, though we would stress that it is not the only one, would be that at much lower levels the pressure itself may cause functional or structural changes which then determine its rate of increase. If this were so, the influence of other factors would be required to initiate the vicious circle. Body weight, for example, could be such a factor, as could perhaps any other temporary cause of sustained raised pressure.

The relationship between the pressure already attained and the rate of increase of pressure (the higher the pressure the greater its rate of increase) may not be one of cause and effect. *If it were found* to be causal, it might have far reaching *implications* regarding therapy. The findings do, however, accord with common experience that many *individuals*[10] and some races[11] show little increase of pressure with age. If they are confirmed by others they would also partially reconcile the divergent views on the nature of essential hypertension.

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REFERENCES

1. Platt, R.: Essential hypertension, incidence course and heredity, Ann. Int. Med. 55:1, 1961.
2. Platt, R.: Heredity in hypertension, Lancet 1:899, 1963.
3. Pickering, G. W.: The nature of essential hypertension, London, 1961, J. & A. Churchill, Ltd.
4. Pickering, G. W.: Hyperpiesis: High blood pressure without evident cause: Essential hypertension, Brit. M. J. 2:959, 1021, 1965.
5. Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The aetiology of essential hypertension. I, II, and IV, Clin. Sc. 13:11, 37, and 273, 1954.
6. Miall, W. E., and Oldham, P. D.: The hereditary factor in arterial blood pressure, Brit. M. J. 1:35, 1963.
7. Johnson, B. C., Epstein, F. H., and Kjelsberg, M. O.: Distributions and familial studies of blood pressure and serum cholesterol in a total community—Tecumseh, Mich., J. Chron. Dis. 18:147, 1965.
8. Miall, W. E., and Lovell, H. G.: Relation between change of blood pressure and age, Brit. M. J. 1:660, 1967.
9. Robinson, S. C., and Brucer, M.: Range of normal pressure: statistical and clinical study of 11,383 persons, Arch. Int. Med. 64:409, 1939.
10. Stamler, J., Lindberg, H. A., Berkson, D. M., Shaffer, A., Miller, W., and Poindexter, A.: Prevalence and incidence of coronary heart disease in strata of the labor force of a Chicago utility company, J. Chron. Dis. 11:405, 1960.
11. Maddocks, I.: Possible absence of essential hypertension in two complete Pacific Island populations, Lancet 2:396, 1961.
12. Lovell, R. R. H.: Blood pressure in Pacific Island populations. Epidemiology: Reports on research and teaching, Pemberton, J., editor, 1963, Oxford University Press.

The effect of posture on the cardiac output during the last six weeks of pregnancy

While measurements of cardiac output in pregnancy date back to 1915, it is only comparatively recently that reliable studies have been made using the Fick principle[1] or dye dilution techniques.[2-6] Most studies have been performed at rest and with the patient in the supine position.

Despite the amount of data that has accumulated, there is still no agreement on the pattern of change in cardiac output during pregnancy. This is due to the fact that the number of women in individual studies has been small and that it has not been possible to perform many estimations in any one individual.

The most widely accepted hypothesis is that cardiac output rises early in pregnancy, reaches peak values about the thirtieth week of gestation, and then falls until at term the cardiac output is similar to that of the nonpregnant woman. The rise in cardiac output is in excess of the metabolic demand of the patient, and the oxygen consumption rises throughout pregnancy and does not fall in the later weeks.[10] The increased cardiac output is not confined to the uterus and placenta, and raised flow has been reported in the skin,[10] the kidney,[11] and perhaps also in the muscle.[14-17] In general, measurement of regional flow has not shown a reduction in the last trimester.

The mechanism for the increased cardiac output is not known. Increased plasma volume[2] and hormonal influences have been suspected[19] and it seems likely that reduction in sympathetic tone is also important.[16] A determining factor may be the need to dissipate heat produced by the increased fetal and maternal metabolism.[16]

Various theories have been suggested to account for the fall in cardiac output in the later months of pregnancy. These have included ageing of the placenta with reduction of placental flow,[20] and the effect of vasopressin.[22,23] None of these theories is entirely satisfactory.

There is evidence, both manometric[24,25] and angiographic,[26] that the gravid uterus compresses the inferior vena cava when the subject is in the supine position, and a study in Belfast was carried out to test if this phenomenon could account for the reported drop in cardiac output.[28] Cardiac output was measured by the Fick principle, mixed venous blood being sampled through a fine polyethylene tube which had been floated into position under pressure control.[29] Cardiac output was measured in a basal state with the patient in the supine position, then in the left lateral position, and again in the supine position. In seven patients in early or midpregnancy (16 to 26 weeks), no significant variation in cardiac output occurred with a change in posture. However, in 12 patients in the last 6 weeks of pregnancy, cardiac output was significantly higher in the left lateral position. The mean cardiac output in the left lateral position was 5.5 L. per minute and in the supine position 4.8 L. per minute, a mean difference of 16 per cent. The fall in cardiac output was not accompanied by a change in heart rate nor with syncopal attacks.

Similar findings have been reported by other

workers.[27,28] Lees and associates[29,30] have found with serial estimations of cardiac output in the lateral position that cardiac output does not fall in the terminal weeks of pregnancy. In one study syncopal attacks occurred.[29] These appear to be due to vasovagal attacks superimposed on the postural fall in cardiac output when the patient lies on her back.

Management of heart disease in pregnancy has been influenced by the belief that the risk of heart failure and pulmonary edema parallels the cardiac output.[8] This risk has therefore been deemed to be less after 32 weeks. If the fall in cardiac output is a postural phenomenon, this conclusion is invalid. Experience at a cardiac clinic in Belfast shows that while the incidence of heart failure and pulmonary edema was highest in the puerperium the incidence of heart failure was greater in the final 6 weeks than at any earlier period of the pregnancy.[25]

In summary, recent studies indicate that the cardiac output varies with position in pregnant women in the last 6 weeks of pregnancy and is significantly lower in the supine subject. This finding may explain the fall in cardiac output in the last 6 weeks of pregnancy noted by most observers.

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REFERENCES

1. Lindhard, J.: Über das minuten Volum des Herzens bei Ruhe und bei Muskelarbeit, Arch. Physiol. 161:233, 1915.
2. Hamilton, H. F. H.: The cardiac output in normal pregnancy as determined by the Cournand right heart catheterization technique, J. Obst. & Gynaec. Brit. Emp. 56:548, 1949.
3. Bader, R. A., Bader, M. E., Rose, D. J., and Braunwald, E.: Hemodynamics at rest and during exercise in normal pregnancy as studied by cardiac catheterization, J. Clin. Invest. 34:1524, 1955.
4. Adams, J. Q.: Cardiovascular physiology in normal pregnancy: Studies with the dye dilution technique, Am. J. Obst. & Gynec. 67:741, 1954.
5. Walters, W. A. W., MacGregor, W. C., and Hills, M.: Cardiac output at rest during pregnancy and the puerperium, Clin. Sc. 30:1, 1966.
6. Hytten, F. E., and Leitch, I.: The physiology of human pregnancy, Oxford, 1964, Blackwell Scientific Publications.
7. Burwell, C. S., and Metcalfe, J.: Heart disease in pregnancy: Physiology and Management, London, 1958, J. and A. Churchill, Ltd.
8. Burwell, C. S.: The placenta as a modified arteriovenous fistula considered in relation to the circulatory adjustments to pregnancy, Am. J. M. Sc. 195:1, 1938.
9. Sonthag, L. W., Reynolds, E. L., and Torbet, V.: The relation of basal metabolic gain during pregnancy to non-pregnant basal metabolism, Am. J. Obst. & Gynec. 48:315, 1944.
10. Palmer, A. J., and Walker, A. H. C.: The maternal circulation in normal pregnancy, J. Obst. & Gynaec. Brit. Emp. 56:537, 1949.
11. Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A.: Circulation during pregnancy, Arch. Int. Med. 62:979, 1938.
12. Burt, C. C.: Peripheral skin temperature in normal pregnancy, Lancet 2:787, 1949.
13. Bucht, H.: Studies on renal function in man with special reference to glomerular filtration and renal plasma flow in pregnancy, Scandinav. J. Clin. & Lab. Invest. 3 (Suppl. 3), 1951.
14. Ginsberg, J., and Duncan, S. L. B.: Peripheral blood flow in normal pregnancy, Cardiovas. Res. 1:132, 1967.
15. Abramson, D. I., Flachs, K., and Fierst, S. M.: Peripheral blood flow during gestation, Am. J. Obst. & Gynec. 45:666, 1943.
16. Herbert, C. M., Banner, E. A., and Wakim, K. G.: Variations in the peripheral circulation during pregnancy, Am. J. Obst. & Gynec. 76:742, 1958.
17. Spetz, S.: Peripheral circulation during normal pregnancy, Acta obst. gynec. Scandinav. 43:309, 1944.
18. Ueland, K., and Parer, J. T.: Effects of estrogens on the cardiovascular system of the ewe, Am. J. Obst. & Gynec. 96:400, 1966.
19. Winner, W.: The role of the placenta in the systemic circulation: a reappraisal, Obst. & Gynec. Surv. 20:545, 1965.
20. McGaughey, H. S.: The cause of the blood and vascular alterations of normal pregnancy and pre-eclampsia-eclampsia, Am. J. Obst. & Gynec. 64:1268, 1952.
21. Roy, S. B., Malkani, P. K., Virik, R., and Bhatia, M. L.: Circulatory effects of pregnancy, Am. J. Obst. & Gynec. 96:221, 1966.
22. McLennan, C. E.: Antecubital and femoral venous pressure in normal and toxemic pregnancy, Am. J. Obst. & Gynec. 45:568, 1943.
23. Scott, D. B., and Kerr, M. G.: Inferior vena cava pressure in late pregnancy, J. Obst. & Gynaec. Brit. Cwlth. 70:1044, 1963.
24. Kerr, M. G., Scott, D. B., and Samuel, E.: Studies of the inferior vena cava in late pregnancy, Brit. M. J. 1:532, 1964.
25. Mulholland, H. C., and Boyle, D. McC.: Brit. Heart J. (to be published).
26. Resnekov, L.: Synchronized capacitor discharge in the management of cardiac arrhythmias with particular reference to the haemodynamic significance of atrial systole, M.D. Thesis, University of Capetown, 1965.
27. Vorys, N., Ullery, J. C., and Hanusek, G. E.: The cardiac output changes in various positions in pregnancy, Am. J. Obst. & Gynec. 82:1312, 1961.
28. Kerr, M. G.: The mechanical effects of the gravid uterus in late pregnancy, J. Obst. & Gynaec. Brit. Cwlth. 72:513, 1965.
29. Lees, M. M., Taylor, S. H., Scott, D. B., and Kerr, M. G.: The circulatory effects of recumbent postural change in late pregnancy, Clin. Sc. 32:453, 1967.
30. Lees, M. M., Taylor, S. H., Scott, D. B., and

Kerr M. G. A study of cardiac output at rest throughout pregnancy, J. Obst. & Gynaec. Brit. Cwlth. 4:319, 1967.
31. Carr F. B. and Hamilton, B. E. Five hundred women with serious heart disease followed through pregnancy and delivery, Am. J. Obst. & Gynec. 21:824, 1933.
32. Boyle D. McC. and Millholland, H. C. (Unpublished.)

Unusual electrocardiogram in meningococcal disease

In a series of 112 consecutive meningococcal infections Wolf and Birbara reported that 20 had abnormal electrocardiograms (ECG's) excluding sinus tachycardia. The most frequent abnormalities were disturbances of cardiac rhythm—that is, wandering pacemaker, nodal rhythm, and occasional premature ventricular contractions. A few patients showed disturbances of the QRS, S-T segments, and T waves. None of the patients demonstrated the unusual ECG pattern encountered in the present case.

A 17-year-old Caucasian basic trainee at Fort Polk, La., developed vomiting, dizziness, generalized muscular weakness, fever, chills, semicoma, petechiae, nuchal rigidity, absent superficial abdominal reflexes, and equivocal bilateral Babinski signs. The cerebrospinal fluid (CSF) was turbid and contained 8,400 cells per cubic millimeter (98 per cent polymorphonuclear leukocytes), sugar 13 mg. per 100 ml., chloride 115 mEq. per liter, protein 333 mg. per 100 ml., and gram-negative diplococci on direct smear. Intravenous crystalline penicillin G (150 mg. per kilogram per day) was administered. Culture of the CSF revealed *Neisseria meningitidis*, Group B. Venous blood and buffy coat cultures were negative.

A 12 lead ECG taken on the day of admission had a normal appearance and a Q-T interval of 0.45 second (Fig. 1). Two days later the ECG revealed symmetrical T-wave inversion in Leads I, V₂, V₃ to V₅ and flattened T waves in V₆ (Fig. 2). The deepest T-wave amplitude was 5 mm. and was recorded in Lead V₃. The Q-T interval was 0.51 second. These changes persisted for the next 12 days. After 13 days the T waves in Leads V₃ to V₅ was less deeply inverted (4 mm.), flattened in V₂, and more upright in V₆. The Q-T interval was 0.47 second. Three days later the T wave was more

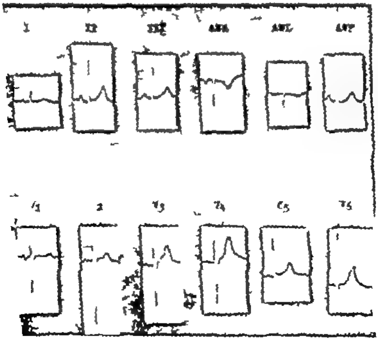

Fig. 1. ECG dated Dec. 2, 1966, showing normal appearance and a Q-T interval of 0.45 second.

Fig 2 ECG dated Dec 4 1966 showing symmetrical T inversion in Leads I V, V to V and flattened T wave V

pright V . One month later the ECG appeared normal and was sim lar t th initial ECG except for decreased mplitude of the positiv T wave in Leads V to V (5 mm compared to 7 mm. in Lead V) and the Q-T interval was 0 44 second.

Repeated cardiac auscultation and serial chest roentgenograms were normal. On the fourth through the sixth hospital days, the serum glutamic oxalacetic transaminase (SGOT) was 40 27 and 20 units the serum lactic acid dehydrogenase was 220 250 nd 320 units and the serum total bilirubi was 0 3 0 4 and 0 3 mg per 100 ml The patient was semicomatose on admission he showed partial phasia and lurred speech by the second day On the fourth day *impaired recent memory was noted* cerebration as normal by the 6th day The patient recovered *completel from the meningococcal* infection.

This patient had an evolutionary ECG pattern consistent w th an acute anterior all subendocardial myocardial infarction, as lasified and defined by Edson, except that the Q-T I terv l was prolonged. One of the eight autopsied cases in th above-mentioned series showed hemorrhagic subendocardial myocardial infarction of the left ventricle. This occurred patient with the meningoencephalitic form who developed respiratory center arrest and was maintained by artificial entilation for one week prior t death. The infarction was probably secondary to hypoxemia and not due directly to the meningococcal infection.

Focal interstitial myocard'tis and/or petechial hemorrhages ere present in the myocardium in seven of the eight autopsied cases. Colonies of diplococci ere present in the myocardi m in one case in add tion, two cases showed minimal focal m ocardial necrobiosis.

ECG changes due to cerebral causes ha been reported. The typical ECG pattern due t cerebral causes consists of prolongation of the Q-T interval more than 120 per cent of normal and tall positiv or deeply negativ T aves with amplitude more than 5 mm *Burch* nd associates, Fink elstein and Nagaboni nd Hugenholtz also described *idening of the* T which suggested incorporation of the U a. Fent and Gorman and Schindler and Sarawace did not find prevalent U waves but these hav been reported b others. *Fentz* nd Gorman and *Porter and associates*[10] described S-T segment deviations as w ll

Serum electrolytes ere *normal in the present* case nd there was no clinical reason to suspect hypocalcemia.

The cause or causes of the serial ECG changes in the present case remain obscure since recovery was complete.

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REFERENCES

1. Wolf, R. E., and Barbara, C. A.: Meningococcal infections at an army training center, Am. J. Med. 44:243, 1968.
2. Edson, J. N.: Subendocardial myocardial infarction, Am. Heart J. 60:323, 1960.
3. Abeles, M. M., and Schneider, D. E.: Electrocardiographic changes during encephalography, Am. J. M. Sc. 190:673, 1935.
4. Bick, M. W., and Epstein, B. S.: Electrocardiographic changes during pneumoencephalography, Am. Heart J. 26:200, 1943.
5. Beyer, E., Ashman, R., and Toth, L. A.: Electrocardiogram with large upright T waves and long Q-T intervals, Am. Heart J. 33:796, 1947.
6. Burch, G. E., Meyers, R., and Abildskov, J. A.: A new electrocardiographic pattern observed in cerebrovascular accidents, Circulation 9:719, 1954.
7. Finkelstein, D., and Vigaglioni, A.: Electrocardiographic alterations after neurosurgical procedures, Am. Heart J. 62:772, 1961.
8. Fentz, V., and Gormsen, J.: Electrocardiographic patterns in patients with cerebrovascular accidents, Circulation 25:22, 1962.
9. Hugenholtz, P. G.: Electrocardiographic abnormalities in cerebral disorders. Report of six cases and review of the literature, Am. Heart J. 63:451, 1962.
10. Porter, R. W., Kamikawa, K., and Greenhoot, J. H.: Persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain, Am. Heart J. 64:815, 1962.
11. Schindler, S. C., and Surawicz, B.: Clinical significance of the ECG pattern with prolonged Q-T interval, and increased T or U amplitude (CVA pattern), Abstracts 16th Annual Scientific Sessions, Am. College Cardiol., 1967, p. 148.

The influence of certain drugs and of prompt squatting on the systolic murmur in hypertrophic obstructive cardiomyopathy

The systolic murmur in hypertrophic obstructive cardiomyopathy (HOCM) begins after the first heart sound, has a crescendo-decrescendo configuration, and has its maximum intensity to the right of the midsystolic point. It is low pitched, best heard in the fourth left intercostal space, and radiates to the apex and base of the heart. It varies markedly in intensity from moment to moment.

There is often a well-heard fourth heart sound, less often a softer third sound. In addition, left and right-sided mid-diastolic ventricular obstructive inflow murmurs may be heard. An aortic early diastolic murmur is occasionally heard—this being due to distention of the aortic ring by asymmetrical hypertrophy.

There are probably several valid reasons for the systolic murmur in this condition. Thus, obliteration within the ventricle, mitral incompetence, and probably turbulence within the strongly and rapidly contracting ventricle may all play their part in its production.

Inhalation of amyl nitrite intensifies the systolic murmur in HOCM and increases the gradient. Phenylephrine abolishes or markedly reduces the murmur and gradient; isoproterenol increases the gradient and the murmur. Thus, the murmur seems to vary in intensity directly with the gradient.

The action of amyl nitrite and phenylephrine cause an opposite effect on the systolic murmur of valvar mitral incompetence: the former diminishes and the latter intensifies the loudness of the bruit.

These findings do not rule out incompetence of the mitral valve as a factor in the production of the systolic murmur—because the cause is not intrinsically mitral valve disease but mitral incompetence secondary to papillary dysfunction due to papillary and septal hypertrophy and the drugs by altering the internal dynamics within the left ventricular chamber could influence the valve mechanism.

In contrast to the marked lessening in intensity or disappearance of the systolic murmur with intravenous phenylephrine, it has been shown that the murmur of aortic stenosis is minimally increased or diminished, thus providing a useful and simple bedside test in differentiating the two conditions.

Prompt squatting provides a simple bedside method of acutely increasing venous return, effective filling pressure of the heart, stroke output, and systemic arterial pressure. Prompt squatting abolished the murmur in 11 cases of HOCM and softened it markedly in seven. In one the murmur softened slightly and in another the effect was variable.

In contrast, in all cases of valvar aortic stenosis and mitral incompetence studied, the systolic murmur increased in loudness.

Prompt squatting intensifies the murmur of pulmonary stenosis. In this condition the sudden

increased venous return would be expected to increase the murmur.

The increase in intensity of the systolic murmur in HOCM can be explained by the sudden increase in venous return leading to increased left ventricular filling and increase in end-diastolic volume.

In addition, the raised arterial pressure and peripheral resistance would reduce the intraventricular gradient and thus the intensity of the murmur.

Prompt squatting has thus proved to be an excellent and simple bedside test in this condition.

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REFERENCES

1. Nellen, M., Gotsman, M. S., Vogelpoel, L., Beck, W., and Schrire, V.: The effect of prompt squatting on the systolic murmur in idiopathic hypertrophic cardiomyopathy, Brit. M. J. 3:140, 1967.
2. Goodwin, J. F.: Disorders of the outflow tract of the left ventricle, Brit. M. J. 2:461, 1967.
3. Vogelpoel, L., Nellen, M., Swanepoel, A., and Schrire, V.: The use of amyl nitrite in the diagnosis of systolic murmurs, Lancet 2:810, 1959.
4. Nellen, M., Beck, W., Vogelpoel, L., Swanepoel, A., and Schrire, V.: The effect of amyl nitrite, phenylephrine, and isoproterenol on the systolic murmur in hypertrophic obstructive cardiomyopathy, South African M. J. 39:304, 1965.
5. Sharpey-Schafer, E. P.: Effects of squatting on the normal and failing circulation, Brit. M. J. 1:693, 1955.

Letter to the Editor

The 'Brody' effect

To the Editor

In their article, pages 642 to 651 of the November 1967 *issue of the* JOURNAL, *Doctors McFee and* Rush refer to the augmentation of radial, and attenuation of tangential, cardiac electromotive forces by the low-resistance intracardiac blood mass, as the "Brody effect." Dr. Mark R. Barber and I (Brit. Heart J. 23:649, 1961) termed the distortion of the lead field induced by "wrapping" multi-electrode grids round the chest wall, instead of mounting them on parallel platforms, the "Brody slope effect." *The confusion resulting from having* two concepts to one eponym could be reduced by adding a modifying term to the more recent one, converting it to say the "Brody inhomogeneity" effect.

Eponyms seem justifiable here as vehicles of concise *description. Also they offer an only too* seldom presenting opportunity to honor one of the most distinguished investigators in this field.

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Book reviews

PULMONARY EMBOLISM By Frank D Gray Jr M D Associate Professor of Medicine Yale University School of Medicine, New Haven, Con Philadelphia, 1966 Lea & Febiger Publishers, 234 pages. Price $8 50

This small book deals primarily but not exclusively with pulmonary embolism of thrombotic origin. The chapters include the following Introduction, The embolus Pathological effects, Pulmonary infarction Physiology Clinical diagnosis, Management The results of embolism (prognosis and sequelae) and Conclusions The text is supplemented with 15 case histories presented separately but interwoven into the text to illustrat various facts and concepts.

This contribution is basically detailed literature review (671 references) interspersed freely with the author own experience This reviewer would disagree t minor degree with several of the nterpretations of the author e.g various aspects of lectrocardiography and the reliability of serum bilirubin and enzyme changes in diagnosis. I am sure that most clinicians reading this book would like to see the inclusion of more high quality illustrations of electrocardiograms chest -rays pulmonary angiograms, and pulmonary radioisotope scans

This book can be recommended with only moderate enthusiasm

A SURGEON'S GUIDE TO CARDIAC DIAGNOSIS Part II The Clinical Picture By Donald N. Ross, Berlin, Heidelberg New York, 1967 Springer Verlag 88 pages Price $6 00

This is an interesting guide to cardiac diagnosis. It consists of 88 pages, including the index The length of the book reflects the brevity of each cardiac state discussed It is ntended for surgeons, but appears to be t a level of nurses. The author in an equally brief foreword states surgeons have largely graduated from the role of operating technicians t that of practical cardiologists This reviewer would vigorously challenge this statement if this "Surgeon guide to cardiac diagnosis reflects their qualifications. This guide should have little use in cardiology and can only give the surgeon false sense of security in cardiac diagnosis to the detriment of the patient.

4TH EUROPEAN CONFERENCE ON MICROCIRCULATION Edited by H Harders Hamburg Basel, 1967 S. Karger AG 548 pages Price $40 60.

This fourth European conference on the microcirculation was held in Cambridge England, in 1966. These proceedings consist of ma y papers on pharmacology lotting phenomena, tissue injury—emboli, microcirculation in special cases, capillary blood flow studies in the pancreas, antigen-antibody reactions, toxic agents and ionizing radiation cerebral microcirculation, biorheology small vessel innervations and reactivity lymphatics, transplant tions, ultrastructure of tissues and injury permeability of vascular endothelium and clinical microcirculation. Most of the papers are short and succinct. However a few are only one page in length, ly abstracts. A would be expected, some of the papers are excellent whereas others are of little value. Nevertheless as the previous publications t is a ery good one and is highly recommended.

ELECTROCARDIOGRAPHY AND VECTORCARDIOGRAPHY By E. Grey Dimond, M D Member of Scripps Clinic and Research Foundation La Jolla, Calif Boston, 1967 Little, Brown & Company 4th edition, 152 pages. Price $7.50

This book has served as the textbook for the electrocardiography course t the University of Kansas School of Medicine for the past 17 years. Perhaps its contents are best described by an excerpt from the Preface to offer small monograph hich can provide a totally uninitiated student or physician with a reasonable understanding of spatial electrocardiography and ectorcardiography and hich can make this understanding linically useful to him. This book has been developed as method of teaching not as a reference text or treatise

There are a number of small monographs available written for this purpose and from the standpoint of scientific content nd suitability for this goal, most are satisfactory Selection of one as superior to another becomes matter largely of personal preference On this basis, this reviewer feels that there are publications which better suit this intended goal than the present book.

PHYSIOLOGY OF HEMOSTASIS AND THROMBOSIS By Shirley A. Johnson Ph.D and Walter H Seegers, Ph D D.Sc., Springfield Ill., 1967 Charles C Thomas Publishers 338 pages. Price $13.75

The proceedings of the fourteenth annual symposium on the physiology of hemostasis and thrombosis represents primarily a discussion of platelets. Among the subjects included are initiation of viscous metamorphosis of the platelets, reactions of human platelets to thrombin, red blood cells fibrin and platelets in hemostasis, plat let aggregation, subcellular platelet parti-

cles, platelet-leukocyte aggregation, plat let shape and aggregation, and ultrastructure of platelets. As in the previous publicatio of the conferences, the subjects discussed have been timely and the contributors actively engaged in a study of the problems of hemostasis and thrombosis. This is an interesting publication. The papers are well written and the illustrations and bibliography good. The book is recommended to those interested in platelets and platelet function and especially thromboembolic phenomena in man.

Rekonstruktive Chirurgie der Arterien. By Priv Doz. Dr med J V llmar and Prof Dr med., Dr med. h.c. Dr jur h.c. F Linder Stuttgart, 1967 Georg Thieme Verlag 416 pages.

This is well-written and nicely illustrated book on reconstructive arterial surgery The authors describe the present methods, indications for surgery aspects of various arterial diseases such as aneurysms, arteriovenous fistulas, obstructive disease pathogenesis, and results. This book is good single volume on rapidly growing subject in surgery As would be expected, the medical aspects of management are neglected. The bibliography is fairly complete. This is good book and is highly recommended for those interested in vascular surgery

Cardiopulmonary Resuscitation Conference Proceedings. Edited by Archer S Gordon M D National Research Council, National Academy of Sciences, National Academy of Engineering. Washington D C., 1967 232 pages. Price $4 75

This publication of the proceedings of a conference on cardiopulmonary resuscitation conducted under the auspices of the National Research Council on May 23 1966 consists of several papers presented along with questions and answers and an appendix illustrating techniques. The presentations are not new but they include in one volume discussions of the methods and common problems in cardiac resuscitation. The illustrations are good the references adequate and the subjects clearly presented. This is very good paper-bound book which should be usef l t nurses and laymen as well as physicians.

Venen Fibel. By Dr med. F Haid-Fischer nd Dr med. Helmut Haid, Stuttgart, 1967 Georg Thieme Verlag, 218 pages.

This book on varicose veins is concerned with the anatomy and physiology of the veins on the legs, diagnosis of diseases of the veins, medical and surgical therapy use of anticoagulants in venous thrombosis, surgical procedures, and prophylaxis. Venous diseases are extremely important in clinical medicine and the authors handle the subject very well. The illustrations are numerous and clear Unfortunately and as would be expected, nothing really new is presented but for those who wish useful compendium on the subject this paper-bound book is recommended.

Books received

Surgery of the Aged and Debilitated Patient By John H. Powers, Philadelphia, 1968, W B Saunders Company 611 pages Price $19 00

Il Fenomeno Di Luciani-Wenckebach By M Ballarino and R. Rumolo Milano, Recordati-Industria Chimica Farmaceutica, 1967 122 pages

Announcement

A FIVE DAY CONGRESS IN CARDIOLOGY will be held in Mexico, Oct 29 through Nov 2 1968 the week after the Olympic Games. The faculty will be composed of Abdo Bisteni, M D Mexico P G F Nixon, M.R C.P London Joseph K. Perloff M D Washington and Jose Ponce de Leon, M D Mexico. The directors will be Demetrio Sodi-Pallares, M D Mexico, and Henry J L. Marriott M D St. Petersburg

For further details write to the Rogers Heart Foundation, 500 First Federal B lding St. Petersburg Fla.

SEVENTH ANNUAL JANE NUGENT COCHEMS COMPETITION The University of Colorado School of Medicine announces the Seventh An ual Cochems Competition with a prize of $2,500 to be awarded t the author of the best paper titled "Thrombophlebitis and Basic Vascular Problems. The problems under consideration should concern underlying mechanisms or processes of vascular disease, particularly those associated with thrombosis but not necessarily restricted t it. All persons holding the doctorate degree and ubject to U S. income tax are eligible Entries in triplicate, including *all* illustrations, charts, etc., are due Nov 15 1968 the winner to be announced early in 1969 Papers submitted may not be published until after announcement of the winner The judges are Dr Michael E. De Bakey Baylor University School of Medicine, and Dr Sol Sherry Temple U iversity School of Medicine. Address all inquiries to the Office of the Dean, University of Colorado School of Medicine, 4200 E. Ninth Avenue, Denver Colo. 80220.

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Editorial

Cerebral apoplexy: Figures and features

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In most countries with reliable medical statistics cerebral apoplexy is the third leading cause of death, and it is the most common and most serious acute nontraumatic neurological disorder. In various countries with equal standards of living deaths from cerebral apoplexy range between 100 and 160 per 100,000 population per year for all age groups, and although the incidence increases in the higher age groups, still 20 per cent of these deaths occur in persons between 45 and 65 years of age. This figure must be considered against the background of the present average duration of life, which is close to 70 years for men and a couple of years higher for women, and more especially against the individual life expectancy at these ages, which is around 14 years for a man of 65 and around 11 years for a man of 70. For women the corresponding figures are two years greater.

Deaths from apoplexy are no measure of the frequency of strokes. This important figure is, in fact, unknown, since strokes are not reported. An estimate of the frequency of fatal and nonfatal strokes in the general population has been made by Dalsgaard-Nielsen, who arrived at a total and probably a minimum frequency of eight to nine per 1,000 persons per year. Is the mortality rate calculated on the basis of this figure and the reported deaths from apoplexy in a population? Some countries (e.g., Canada) will have a mortality rate for strokes in a population of slightly below 10 per cent, and others (e.g., Denmark) around 20 per cent. In 1,000 hospitalized patients the mortality rate was 44 per cent, and between 35 and 50 per cent of patients with cerebral apoplexy will die with their first attack.

Permanent disability is the most common result of nonfatal strokes. In the 1,000 hospitalized patients just mentioned less than one per cent of the survivors were classified as "not disabled," while 66 per cent were "heavily disabled" following the stroke. In another series of consecutive hospitalized patients nearly two thirds were able-bodied until the stroke.

Although these figures probably do not give the full truth, they represent important aspects of it, and they illustrate the serious import of the problems related to the cerebral apoplexy. This term is, in the official medical statistics, used as a diagnosis. It should be emphasized, however, that cerebral apoplexy is a syndrome common to a variety of cerebral lesions

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and that as a final diagnosis, it has the same value or lack of value as acute abdomen

In contrast to the many different clinical patterns, the typical postmortem findings are completely dominated by two lesions—the cerebral infarction and the cerebral hemorrhage For this latter intracerebral hematoma is a preferable term since we are dealing with the static result of the hemorrhage i e the intracerebral clot, and not with the bleeding itself In fatal strokes, the incidence of hematoma and infarction seem to be identical but the peak for the incidence of hematoma is found in the age group 50 to 60 while that for infarction is in the age group 60 to 70 Fifty per cent of fatal hematomas in patients over 40 years of age seem to occur before the age of 60

It is of course not permissible to apply these figures directly to the patients surviving a stroke and it becomes obviously *misleading to do so when it is realized* that the differentiation between infarction and hematoma fails in about 40 per cent when based upon clinical signs and symptoms alone[3] Electroencephalography is of little or no help to the differential diagnosis and the same holds true for the isotope scanning Lumbar puncture is directly misleading if a hemorrhagic spinal fluid is taken as indicating the presence of an intracerebral hematoma. A prerequisite for a bloody spinal fluid is (when a traumatic puncture is left out of consideration) a contact between the CSF and a hemorrhagic brain lesion But this lesion may be a hematoma or a hemorrhagic infarction and both of these lesions may later give rise to xanthochromic spinal fluid A colorless spinal fluid is seen if an intracerebral clot is located within the white matter of the brain without contact with the cerebrospinal fluid (CSF) in the ventricles and the cerebral subarachnoid space. These hematomas are not infrequent and are, furthermore often favorable objects for operation Regarding the spinal fluid pressure this may be high in infarctions with associated cerebral edema and normal even in sizable intracerebral hematomas.

It is not surprising that, under these diagnostically unfavorable circumstances, therapy could not be directed against the cerebral lesions themselves but only against their sequelae. The introduction however of first and foremost, the cerebral angiography into the routine examinations of stroke patients[4] represented a considerable improvement of both diagnostic and therapeutical possibilities. We now know that infarctions are much more frequent than hematomas that about half of the infarctions are caused by angiographically demonstrable arterial occlusions of which about 50 per cent are not intracranial but located in the internal carotid at its origin in the neck that several intracerebral hematomas are located laterally in the hemispheres and do not destroy the basal ganglia and that a small but not negligible number of strokes are caused by other lesions e.g tumors and subdural hematomas In addition much important knowledge of the collateral circulation systems in the brain has been obtained The better diagnostic possibilities have given rise to *increased therapeutic activity first and* foremost on the surgical front. Endarterectomy in patients with extracranial atheromatous narrowing of the internal carotid has long proved successful if based on careful selection and even patients with total occlusion of one internal carotid may although rarely benefit from vascular operation[7] A prerequisite for diagnosis for selection for surgery for the surgical tactics and for the postoperative evaluation of the result is a careful angiographical study including also the thoracic origin of the cerebral arteries.

Intracerebral hematomas are space taking lesions, acting not only by local destruction of brain tissue, but also through the associated more or less widespread cerebral edema with consequent impairment of the cerebral circulation with distortion and displacement of the brain stem and consequent endangering of vital functions.

Clinically and anatomically two types of hematomas may be distinguished The first is the classical internal capsule bleeding" where the focal tissue destruction hits the high concentration of nuclei and pathways in and around the basal ganglia and the hypothalamus. This is clinically characterized by acute onset severe initial impairment of consciousness often coma dilated fixed pupils, decereb-

rate rigidity, and hemorrhagic spinal fluid under increased pressure. This lesion is the common end of patients with a history of malignant vascular disease—hypertensive, renal or diabetic, and surgical removal of the hematoma is of no value.

The other type of hematoma is located within the white matter of the hemispheres without, or with little involvement of the basal ganglia. Clinically, these hematomas correspond very often to the classical concept of a cerebral thrombosis. The onset is often subacute or even slow, with a development over several hours. Impairment of consciousness is less severe and may even be lacking initially. Normal blood pressure or a history of slight nonmalignant hypertension is not infrequent and malignant hypertension and other severe vascular diseases are relatively rare. Colorless spinal fluid is found in 30 per cent of these patients, and even the intracranial pressure may be normal despite the presence of a hematoma of 100 c.c. or more. These hematomas often produce little local destruction of brain tissue but are more prone to split the fiber tracks, and may therefore be removed with very satisfactory results. If located in the posterior third of the cerebral hemispheres, they may escape detection in the angiogram, but will be clearly visible in the ventriculogram.

The concept of cerebral apoplexy is, by tradition, connected with an idea of something hopeless affecting old and decrepit individuals. When used as a diagnosis it exerts an unfavorable influence on diagnostic and therapeutic activity and consequently represents a discrimination of patients in the older age groups. Modern medical terminology would do well without this term, which should be replaced by terms telling about the nature and the location of the cerebral lesions. This is possible only by means of the technical diagnostic procedures which have long proved indispensable to modern neurology. It is necessary to realize that more and more people will belong to the exposed age groups, and that these acute and often emergency neurological problems represent an increasing obligation and challenge to both research workers and clinicians.

REFERENCES

1. Riishede, J.: Cerebral apoplexy. Statistical and diagnostic considerations, Canad. M. A. J. 97:151, 1967.
2. Dalsgaard-Nielsen, T.: 1,000 tilfælde af apoplexia cerebri, Nord. Med. 54:1677, 1955.
3. Dalsgaard-Nielsen, T.: Some clinical experience in the treatment of cerebral apoplexy, Acta psychiat. & neurol. scandinav. (Suppl.) 108:101, 1956.
4. Robinson, R. W., Cohen, W. D., Higano, N., Meyer, R., Lukowski, G. H., McLaughlin, R. B., and MacGilpin, H. H.: Life-table analysis of survival after cerebral thrombosis, J.A.M.A. 169:1149, 1959.
5. Riishede, J.: Cerebral apoplexy. An arteriographical and clinical study of 100 cases, Acta psychiat. & neurol. scandinav. (Suppl.) 118:151, 1957.
6. Riishede, J.: Cerebral apoplexy. Statistical considerations, Acta psychiat. & neurol. scandinav. (Suppl.) 108:347, 1956.
7. Lougheed, W. M., Elgie, R. G., and Barnett, H. J. M.: The results of surgical management of extracranial internal carotid artery occlusion and stenosis, Canad. M. A. J. 95:1279, 1966.

Vectorcardiographic aspects of primary myocardial disease in 50 patients

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The vectorcardiographic aspects of primary myocardial disease (PMD) have received little attention in the medical literature Farrokh and co-workers[1] commented on the vectorcardiograms (VCG s) in four patients with amyloid heart disease Féhér and associates[2] described the VCG s associated with Chagas myocardiopathy with special reference to patients with superiorly oriented vector loops. The vectorcardiographic findings in nine patients with idiopathic hypertrophic subaortic stenosis was reported by Estes and associates. Karry and colleagues[4] reported the vectorcardiographic findings in 14 members of three families with familial myocardiopathy Banta and Estes[5] reported the VCG s in 11 patients with idiopathic myocardial hypertrophy The only larger series of patients reported with PMD was that by Horan and co-workers. These authors reported the VCG s in 25 patients with idiopathic myocardiopathy During the past three years, we have followed and studied a group of patients with PMD One aspect of this prospective study has been an evaluation of the VCG The results of this study form the basis for this report

Material and methods

We have studied 60 patients with cardiomegaly but without any evidence for hypertensive coronary artery rheumatic, congenital or pericardial disease Patients with obstructive cardiomyopathy were intentionally eliminated A total of 50 patients had VCG s available for review and form the basis for this presentation The patients were seen and evaluated at either The Queens Hospital Center a municipal hospital or at The Long Island Jewish Hospital a nonprofit voluntary hospital The group of patients had an average age of 44 ± 8 4 years and consisted of 35 men and 15 women There were 34 Negroes and 16 Caucasians. The average duration of symptoms was 3 8 ± 1 02 years. Three patients were asymptomatic and were seen because of unexplained cardiomegaly Diagnostic cardiac catheterization was performed on 41 patients and included selective coronary angiograms in eight patients. These studies failed to reveal any evidence of rheumatic congenital or coronary artery disease The classification of these 50 patients included alcoholic cardiomyopathy in 16 patients familial cardiomyopathy in four patients

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and a possible familial basis in three other patients (it should be noted that, of these seven patients, three were chronic alcoholics, which made classification difficult) two patients had a past history of myocarditis and were apparently left with an enlarged heart and 25 patients were classified as idiopathic. Of these 50 patients 18 have since died and postmortem reports were obtained on eight, confirming the presence of PMD

Spatial VCG's were taken on an Electronics for Medicine multi-channel oscillographic recorder using the Frank system of electrode placement. The vector loop was interrupted 500 times per second In all tracings the inscription was interrupted by the pointed end of the time dash The VCG's were analyzed in the frontal horizontal and right sagittal plane projections (Fig 1) in all cases, with the notation of Helm[8] The X, Y and Z axes are indicated in Fig 1 The direction of the initial 0 01 msec. vector was found to be more easily defined by recording orthogonal X Y Z leads at a paper speed of 100 mm. per second The vectorcardiographic interpretation of left ventricular hypertrophy[8] left bundle branch block,[9] and right bundle branch block was based on criteria described by other workers using the Frank lead system A minimum of 2 0 mv for the maximum QRS vector in any reference plane was required for the diagnosis of left ventricular hypertrophy The location and amplitude of the maximum QRS vector was determined in all planes, the normal values for these being based on the results of Forkner and associates[10] and Bristow[11] respectively The ST vector and the T loop were evaluated by obtaining the highest possible amplification around the "E" point

Results

The initial 0 01 msec. vector in the horizontal plane (Fig 2) in the majority of patients was directed to the left and anterior In only 14 patients (28 per cent) were the initial forces directed to the right and anterior In one patient the 0 01 msec. vector was oriented to the right and posterior A selective coronary angiogram in this 39-year-old man was normal. Another patient a 47 year-old Negro man whose 32 year-old brother died of congestive heart failure with unexplained cardiomegaly had the initial forces directed to the left and posterior This patient also had a normal selective coronary angiogram and postmortem examination revealed normal coronary vessels.

The VCG's of these 50 patients were separated into two groups depending on the location of the QRS vector loop in the frontal plane (Fig 3) Group I consisted of 28 patients with the major portion of the QRS loop and the maximum QRS vector below the X axis in the frontal plane. The QRS loop rotated either clockwise or counterclockwise and only occasionally had a figure-of-eight configuration Group II consisted of 22 patients

Fig 1 Reference system (degrees and X, Y Z notation) in the three vector planes.

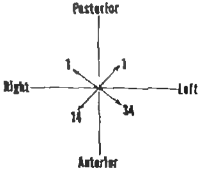

Fig 2 The distribution of the initial 0.01 msec. vector as noted in the horizontal plane.

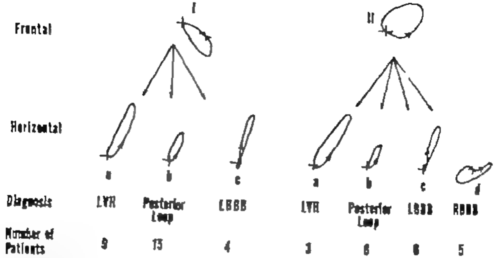

Fig 3 The two groups (Group I and II) of vector loop with the various types (Types a, b and d) observed in the 50 patients with PMD

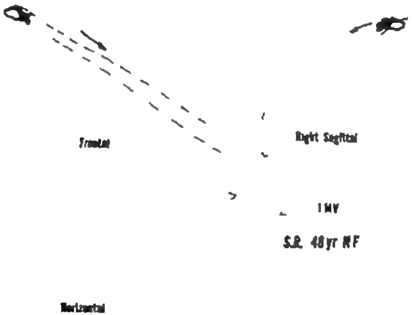

Fig 4 VCG demonstrating left ventricular hypertrophy (Type I). Note figure-of-eight configuration with small proximal counterclockwise loop the horizontal plane.

with the major portion of the QRS loop and the maximum QRS vector located above the X axis in the frontal plane In all cases but one the loop was entirely counterclockwise the exception was one case with a figure-of-eight configuration of which the major proximal portion had a counterclockwise rotation

The specific vectorcardiographic diagnosis of these two groups was made in all cases on the basis of the horizontal loop (Fig 3) In Group I there were nine pa

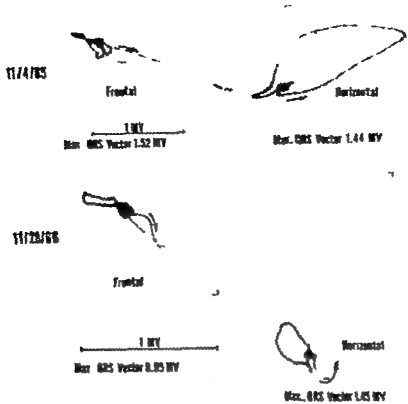

Fig. 5. W. D., 34-year-old Negro man. Serial VCG demonstrating posterior shift of the QRS vector in the horizontal plane (Type Ib). Note that there is no change in the magnitude of the maximum QRS vector in the horizontal plane whereas the maximum QRS vector in the frontal plane has decreased.

tients with left ventricular hypertrophy (Type Ia). In five of these patients, the horizontal loop had a figure-of-eight configuration: four patients had a small counterclockwise proximal segment (Fig. 4) and one had a small clockwise distal segment. The remaining four patients had an entirely counterclockwise loop. In 15 patients lacking voltage criteria for left ventricular hypertrophy, the loop was directed posteriorly (Type Ib). The maximum QRS vector in this group was oriented between 280 to 330 degrees with a mean of 295 ± 23 degrees. Eight patients with Type Ib vectors had a figure-of-eight configuration, the proximal segment always being counterclockwise. An example of Type Ib VCG is shown in Fig. 5. In this patient, serial VCGs were obtained over a one year period and demonstrated a posterior shift of the QRS loop toward the "Z" axis. The posterior shift resulted in a 50 degree displacement of the maximum QRS vector in the horizontal plane without any change in the magnitude of this vector, i.e., in 1965 and in 1966 the maximum QRS vectors in the horizontal plane were 1.44 and 1.45 mv., respectively. As a result of this rotation, the projection of the maximum QRS vector on the X axis became smaller, i.e., the maximum QRS vector in the frontal plane was 1.52 mv. in 1965 whereas in 1966 it was 0.95 mv. This posterior shift of the horizontal loop with a loss of electrical forces displayed on the Y and X axis has been rather striking and has as its electrocardiographic counterpart low voltage in the standard and unipolar limb leads with normal voltage in the precordial leads (Fig. 6). The electrocardiogram (ECG) may be interpreted as indicative of left ventricular hypertrophy because of deep S waves in the right precordial leads. Fig.

7 shows another example of Type Ib vector loop with a small frontal loop the major electrical forces again being displayed on the Z axis. Also note that the major portion of the horizontal loop has a clockwise rotation This patient at the age of 27 was noted to have cardiomegaly and over the next seven years has had congestive heart failure arrhythmias, and multiple emboli The remaining four patients in Group I had left bundle branch block (Type Ic)

In Group II were three patients with left ventricular hypertrophy (Type IIa) two of whom had figure-of-eight configuration with a small counterclockwise proximal segment. Eight patients had posteriorly oriented loops but did not meet voltage criteria for left ventricular hypertrophy (Type IIb) The maximum QRS vector was oriented between 275 to 340 degrees with a mean of 307 $\pm$ 19 degrees The horizontal loop in three patients had figure-of-eight configuration with a counterclockwise proximal loop (Fig 8) Type IIc vectors were counterclockwise superior in the frontal plane with a left bundle branch block pattern seen in six patients. Five patients had terminal conduction delays to the right and anterior indicative of right bundle branch block (Type IId) All these patients with right bundle branch block had leftwards afferent limbs four patients had a clockwise anterior rotation (Fig 9) and one had a counterclockwise posterior rotation In one patient included in Type IId the initial forces revealed slow conduction to the right superior and posterior (Fig 10) The ECG in this patient revealed a P R interval of 0.20 sec This VCG with initial slow conduction is characteristic of intrainfarction block.[14] The patient a 39-year-old Caucasian man with an enlarged heart for five years and no history suggestive of coronary artery disease, had a normal selective coronary angiogram

The distribution of the maximum QRS vector in each plane for the entire group of patients (the horizontal and right sagittal planes do not contain Group IId) is shown in Fig 11 and reveals a tendency for the maximum vector to be superior and posterior The arrow in the figure represents the normal mean and the shaded area encompasses one standard deviation (S. D) of the mean. The mean of the QRS maximum vector for the entire group in the frontal plane was 358 $\pm$ 40 degrees. The mean QRS maximum vector in the

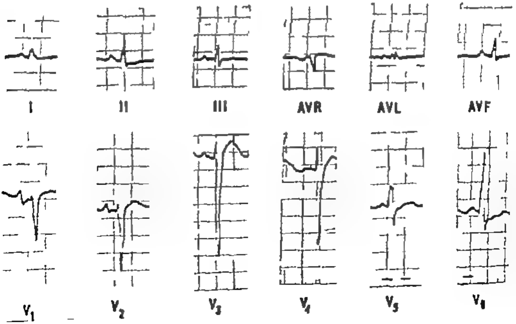

Fig 6 ECG of R D a 34-year-old Negro man, dated Dec. 1 1966, demonstrating low voltage in the standard and unipolar limb leads and normal voltage in the precordial leads. This ECG corresponds to the VCG in Fig 5.

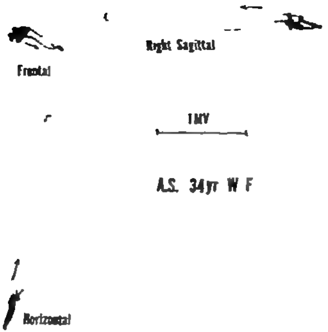

Fig. 7. VCG of Type Ib demonstrating small frontal loop with the major QRS forces being displayed on the "Z" axis of the horizontal and right sagittal planes.

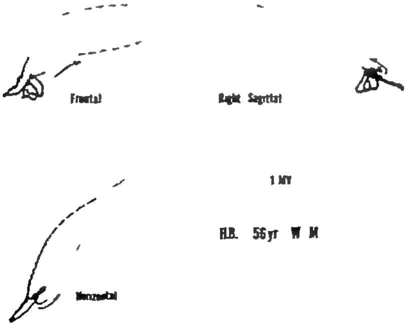

Fig. 8. VCG demonstrating counterclockwise superior frontal loop and figure-of-eight posterior horizontal loop (Type IIb).

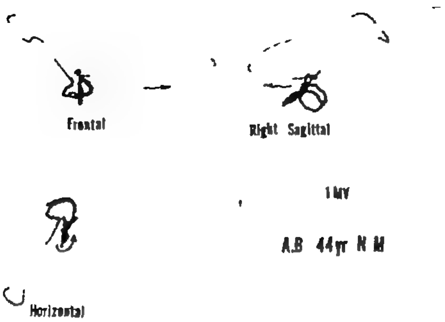

Fig 9 VCG illustrating Type IId vector i.e., right bundle branch block with a superior counterclock wise frontal loop.

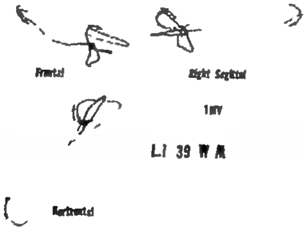

Fig 10 Unusual example of initial and terminal conduction delay with a superior frontal loop Initial forces are to the right, superior and posterior suggesting an inferior and anterior myocardial infarction with intra-infarction block. Selective coronary cineangiogram was normal.

horizontal and right sagittal planes exclusive of Group IId was 304 ± 22.4 degrees and 172 ± 23 6 degrees, respectively Fig 17 shows the distribution for the entire group, exclusive of Group IId of the amplitude of the maximum QRS vector in all planes with the shaded area enclosing one S D of the normal mean The vector loops for almost the entire group tended to be narrow having a length-width ratio in all planes generally greater than four The mean length-width ratio for the frontal horizontal and right sagittal was 7 6 4 0 and 7 6 respectively In many instances, closely timed dashes appeared to indicate conduction delay however only

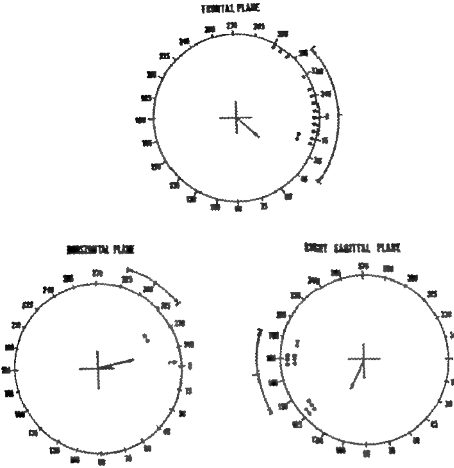

Fig. 11. The distribution of the maximum QRS vector in each plane. The enclosed arrow and shaded area in each plane indicate the mean and 1 S.D. of the mean, respectively, of normal population. The mean of the patients in the present series is indicated by line on the outer arc with arrows enclosing one standard deviation. (Note that the horizontal and right sagittal plane does not include the fi patient in Type IId right bundle branch block with superior counterclockwise frontal loop.)

in the groups designated as left or right bundle branch block was thus more than a subjective impression.

The QRS loop failed to return to the E point in 62 per cent of the patients which indicated the presence of an ST vector. In all of the cases, the ST vector was directed to the right, being anterior in 14 patients and posterior in 17 patients. The T loop was discordant to the QRS loop in the majority of patients, being mainly directed to the right and anterior in 6 per cent of the patients. The T loop was directed to the left and anterior and to the right and posterior in 18 and 8 per cent of the patients, respectively. In six patients, the T loop was directed to the left and posterior in five wherein right bundle branch block was present. The T loop tended to be elongated in all planes and to rotate in a manner similar to that of the proximal portion of the QRS loop. The rotation of the T loop, exclusive of the patients with right bundle branch block, was counterclockwise (80 per cent) in the horizontal and clockwise (88 per cent) in the right sagittal plane. In the frontal plane only 55 per cent of the cases had a clockwise rotation of the T loop. In the patients with right bundle branch block, the T loop rotated clockwise in the horizontal and counterclockwise in the

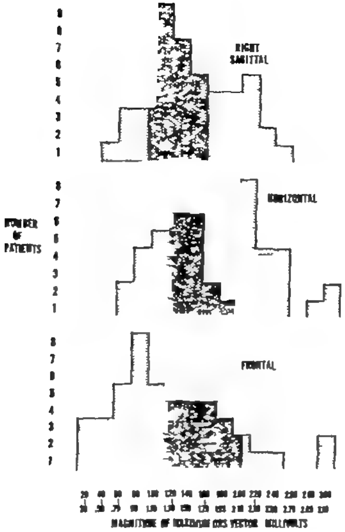

Fig. 12. Distribution of the magnitude of the maximum QRS vector in each plane exclusive of Type IId. The shaded area encloses 1 S.D. of normal population.

right sagittal plane in all five cases. In the frontal plane the T loop rotated counterclockwise in four of the five patients.

Discussion

The various types of VCG's present in these 50 patients are probably a reflection of varying degrees of myocardial hypertrophy, fibrosis, and degeneration. The attempt to classify these vectorcardiographic patterns into two general groups is based on our experience in reviewing serial ECG's in some of our patients. These ECG's have demonstrated changes which indicate a superior and posterior shift of electrical forces and would therefore suggest that in time some patients in Group I will change to Group II. This may indicate a longer duration of disease in Group II. This, in part, is supported by the work of Kariv and associates[4] who noted in 14 members from three families with familial myocardiopathy a posterior shift with a decrease in leftward forces in the horizontal plane with advanced age groups. In one of our patients (Fig. 5) in Group Ib VCG's taken a year apart demonstrated these changes. The patient died one month after the last VCG. Other patients are being followed to evaluate the significance of any vectorcardiographic changes as related to their clinical course. Further ex

perience will be required to justify such a classification.

The normal 0.01 msec. vector in the horizontal plane is directed to the right and anterior[14] due to early depolarization of the mid left surface of the interventricular septum. In 68 per cent of our cases the initial forces were directed to the left and anterior. Kariv and associates[8] observed in patients with familial cardiomyopathy that the younger patients had normally directed septal forces. However with advancing age groups the initial forces shifted left and anterior. As discussed by Sanchez and co-workers[17] loss of these normal initial forces may be explained either by loss of septal muscle tissue as a result of fibrosis or by cancellation from simultaneous activated muscle as a result of hypertrophy of the free left ventricular wall. Either may explain the absence of normal septal forces occasionally found in left ventricular hypertrophy. Rotational changes involving the interventricular septum may also explain the absence of initial septal forces found in left ventricular hypertrophy. If the right septal surface is parallel to the frontal plane or facing slightly leftward the initial 0.01 msec. vector may not be normally directed. In 12 patients in the present series with left ventricular hypertrophy (Type Ia and IIa) four had initial forces direct to the left and anterior. In 11 patients, initial left and anterior forces were associated with left and right bundle branch block. In the 23 patients with a posteriorly oriented loop (Type Ib and IIb) 19 had an initial 0.01 msec. vector directed to the left and anterior and one patient had initial forces to the left and posterior. The latter patient had a normal coronary angiogram. The absence of normal septal forces in Type Ib and IIb together with a posterior directed loop and a figure-of-eight configuration would indicate, according to Sanchez and colleagues, incomplete left bundle branch block.

For the entire group of patients exclusive of those with right bundle branch block, there was a tendency for the maximum QRS to be abnormally posterior (Fig. 11). Horan and associates, using the McFee Parungao vectorcardiographic lead system, also noted that in patients with idiopathic cardiomyopathy the mean orientation of the vector loop when compared to a normal group was more posterior. Furthermore, these authors noted that the spatial orientation of the mean axis of the QRS loop was not only abnormally posterior but also equatorially oriented, i.e., approximates the plane formed by the X and Z axis. This was also noted in our group of patients. In Fig. 11 it will be noted that the mean QRS vector in the frontal plane is 358 degrees (X axis equals 360 degrees) and in the right sagittal plane is 172 degrees (Z axis equals 180 degrees). The VCG's reported by Banta and Estes[3] also demonstrate markedly posteriorly directed QRS vector loops in the horizontal plane. Their 11 patients also were characterized by long narrow loops directed posterior along the Z axis in the sagittal plane. Horan and associates[6] also noted narrow loops especially in the frontal and sagittal planes. This was also noted in our patients. Because of the posterior loops directed on the Z' axis it would be anticipated that the vector planes having the Z' axis as a component will reflect the greatest voltage. This is demonstrated in Fig. 12 showing the distribution of the maximum QRS vector in each plane for the entire group exclusive of Type IId. It will be noted that, in the right sagittal and horizontal plane, the majority of patients have normal or increased voltage of their maximum QRS vector, whereas in the frontal plane the magnitude of the maximum QRS vector is diminished (53 per cent of the patients) or normal. As previously mentioned the ECG's in these patients generally demonstrated normal voltage in the precordial leads with many patients having low voltage in the standard and unipolar limb leads.

The ST vector and the T wave changes noted in these patients are probably secondary to the QRS abnormalities present. The T loop is normally directed to the left and slightly anterior[20] whereas in the majority of the patients in the present series it was oriented to the right and anterior. It is interesting that the T loop rotated normally in the horizontal and right sagittal plane whereas in the frontal plane only 55 per cent of the cases have a normal clockwise

rotation of the T loop In a study of 55 normal patients, the T loop always had a clockwise rotation in the frontal plane.[20] As already noted the T loop tended to have a rotation similar to that of the proximal portion of the QRS loop The finding of counterclockwise rotation of the T loop in the frontal plane in 45 per cent of the cases was directly related to the presence of a superior counterclockwise frontal QRS loop in 44 per cent of the patients. The observation that the T loop was directed to the left and posterior in the patients with right bundle branch block is the usual finding in this conduction disturbance.[21] Also the presence of a clockwise horizontal and counterclockwise right sagittal T loop is also typical for this situation.[21] However a counterclockwise T in the frontal plane is uncommon and here again it is probably related to the superior counterclockwise frontal QRS loop in these patients.

Final comments should be made of the five patients in group IId i.e. VCG's demonstrating right bundle branch block and a superiorly oriented frontal loop This type of vector loop is not unusual in chronic Chagas myocarditis[2] in which right bundle branch block is very common. Saltzman and associates[22] reported similar vector loops in 23 patients with arteriosclerotic heart disease. They classified patients according to the rotation in the horizontal loop Type A had a counterclockwise posterior rotation and Type B had a clockwise anterior rotation In the present series were four patients these authors would classify as Type B and one patient as Type A. Of the four patients in Type B one died suddenly and two are doing poorly The patient with Type A vector is mildly symptomatic experiencing recurrent palpitations. Admittedly the number is small but the observation by Saltzman and associates[22] would suggest that patients with Type B vectors appear clinically to have more extensive myocardial disease and a poorer prognosis.

Summary

The VCG's of 50 patients with PMD is presented The vector loops were classified into two general groups A percentage of 56 of the patients had normal frontal loops (Group I) and 44 per cent had superior frontal loops (Group II) In each group the various types of vector loops were defined by the horizontal vector loop In Group I 18 per cent had left ventricular hypertrophy (Type Ia) 30 per cent had posterior loops (Type Ib) and eight per cent had left bundle branch block (Type Ic) In Group II 6 per cent had left ventricular hypertrophy (Type IIa) 16 per cent had posterior loops (Type IIb) 12 per cent had left bundle branch block (Type IIc) and 10 per cent had right bundle branch block (Type IId)

Characteristic features of the entire group exclusive of Type IId included a posteriorly oriented loop directed toward the Z' axis and relatively narrow loops especially in the frontal and right sagittal plane These features although nondiagnostic appear characteristic for the group of patients with PMD

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REFERENCES

1. Farrokh A. Walsh, T J and Massie, E. Amyloid heart disease. Am. J Cardiol 13 750, 1964
2. Féhér J Pileggi, F Tenceira, V Tranchesi, J Pinto Lima, F V. Spiritus, O Chansky M and Decourt, L I The vectorcardiogram in chronic Chagas myocarditis. A analysis of the intraventricular conduction delay associated with superior oriented ÂQRS. Am. J Cardiol. 5:449 1960.
3. Estes, E. H Whalen R. E Roberts, S R., J and McIntosh, H D The electrocardiographic and vectorcardiographic findings in idiopathic hypertrophic subaortic stenosis, Am Heart J 65:155 1963.
4. Karry I Sherf L and Solomon, M F mural cardiomyopathy With special consideration of electrocardiographic and vectorcardiographic findings, Am. J Cardiol. 13 734 1964
5. Bauta, D H and Estes, E. H Electrocardiographic and vectorcardiographic findings in patient with idiopathic myocardial hypertrophy Am. J Cardiol 14:218, 1964
6. Horan, L. G., Flowers, N C., Thomas, J R and Tolleson, W J The spatial vectorcardiogram in idiopathic cardiomyopathy Progr Cardiovas. Dis. 7:115 1964.
7. Frank, E. A accurate clinically practical system for spatial vectorcardiography Circulation 13 737 1956.

8. Helm, R A Vectorcardiographic notation Circulation 13:581 1956.
9 Wallace, A. G., McCall, B W and Estes, E. H The vectorcardiogram in left ventricular hypertrophy A study using the Frank lead system, AM. HEART J 63:466 1962
10 Neuman, J Blackaller J Tobin, J R., Szanto, P B and Gunnar R. M The spatial vectorcardiogram in left bundle branch block, Am. J Cardiol. 16:352, 1965
11 Baydar I D Walsh T F and Massie, E. A. A vectorcardiographic study of right bundle block with the Frank lead system. Clinical correlation in ventricular hypertrophy and chronic pulmonary disease, Am. J Cardiol. 15:185 1965
12. Forkner C E., Hugenholtz, P G., and Levine, H D The vectorcardiogram in normal young adults, Frank lead system, AM. HEART J 62:237 1961
13. Bristow J D A study of the normal Frank vectorcardiograms, AM. HEART J 61:242 1961
14 Castellanos, A., J Lemberg, L., Ioannides, G., and Saldaneck, L. The vectorcardiogram in right bundle branch block coexisting with left ventricular focal block, Am. J Cardiol. 18 705 1966.
15. Gunther L., and Graf W S The normal and lt spatial vectorcardiogram The time sequence of inscription of the QRSsE of the cube and Frank system Am J Cardiol. 15:656, 1965
16. Sodi Pollares, D Brancato, R. W Pileggi, F Medrano, G A., Bisteni, A., and Barbato, E. The ventricular activation and vector cardiographic curve, AM HEART J 54:498, 1958.
17 Sanchez, C., Walsh, T J and Massie, E. The vectorcardiogram in incomplete left bundle branch block, Am. J Cardiol. 7:629 1961
18. Varriale, D Alfenito, J C and Kennedy R. J The vectorcardiogram of left ventricular hypertrophy Analysis and criteria (Frank lead system) Circulation 33:569 1966.
19 Bristow J D Porter G. A., and Griswold, H E. Observations with the Frank system of vectorcardiography in left ventricular hypertrophy AM. HEART J 62:621 1961
20. Hamby R. I Hoffman, I and Glassman, E. The T loop in right ventricular hypertrophy To be published.
21 Personal observation.
22. Saltzman, P Liem, H and Pick, A. P Right bundle branch block with left axis deviation, Brit. Heart J 28 703 1966.

Electrocardiographic aspects of primary myocardial disease in 60 patients

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The diagnosis of primary myocardial disease in any patient requires the absence of clinical evidence for rheumatic, pericardial, coronary artery, or hypertensive etiology to explain the patient's cardiac disability. In the literature, various terms are used in discussions of patients with such unexplained heart disease. These include myocardosis,[1] idiopathic myocardiopathy, idiopathic heart disease, idiopathic myocardial hypertrophy, obscure cardiopathy,[4] and cryptogenic heart disease.[6] We prefer, with others,[7-10] to classify these patients as "PMD," since this implies no etiology, but does indicate that the myocardium itself is involved in some form of pathological change. The etiology in most cases, even after extensive clinical evaluation, is usually obscure and even postmortem examination in most instances is nondiagnostic. PMD, in essence, is an unexplained myocardial disease, in some cases the common end result of a heterogeneous group of etiologies affecting the myocardium.[7-12] The clinical picture is usually characterized by cardiomegaly, congestive heart failure, thromboembolic phenomena, and arrhythmias.[7,8,12] Some patients demonstrate a familial picture with a greater tendency toward sudden death.[11]

During the past three years, we have studied a group of patients with PMD and followed them closely in a special clinic designed for intensive outpatient care. Part of this study included inpatient laboratory investigation, such as cardiac catheterization, selective coronary angiography, electrocardiogram (ECG), vectorcardiogram (VCG), phonocardiogram, and extensive blood tests. The object of this report is to present our experience with the electrocardiographic findings in this group of patients with PMD.

Material and methods

During the three-year period (April, 1964, to April, 1967), we encountered 81 patients initially seen because of unexplained cardiomegaly. After more intensive evaluation, 21 patients were rejected for reasons noted in Table I. Four patients with complicating bronchopulmonary disease despite evidence of diffuse myocardial disturbance were eliminated. Five patients with obstructive cardiomyopathy were

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Table I

Total patients seen because of unexplained cardiomegaly		81
Deleted patients		21
Complicating bronchopulmonary disease	4	
Obstructive myocardiopathy	5	
Hyperkinetic heart syndrome	3	
Inadequate evaluation	9	
Primary myocardial disease		60
Alcoholic myocardiopathy	19	
Familial myocardiopathy	7	
Possible familial myocardiopathy	4	
Postmyocarditis	2	
Postpartum heart disease	2	
Idiopathic myocardiopathy	26	

Table II. Age distribution of the 60 patients

Age (yrs.)	N
20 to 29	3
30 to 39	15
40 to 49	21
50 to 59	19
60 to 65	2

not included since this group represents a well-defined type in terms of hemodynamic disturbance[11] and electrocardiographic findings. In three patients with enlarged hearts, two of whom presented with congestive heart failure, further study revealed them to have the hyperkinetic heart syndrome as defined by Gorlin.[12] Nine patients could not be evaluated thoroughly. The 60 remaining patients had no clinical evidence of any hypertensive, coronary artery, rheumatic, or pericardial disease and, furthermore, had no complicating factor which would make evaluation difficult. The 60 patients were seen and evaluated at either The Queens Hospital Center, a municipal hospital, or at The Long Island Jewish Hospital, a voluntary nonprofit hospital. All patients had cardiomegaly and 57 patients when initially seen were admitted to the hospital because of symptoms referable to their cardiovascular system. The majority of patients entered in congestive heart failure. A total of 34 patients were seen by one of the authors (R. I. H.).

Table II shows the age distribution of these patients at the time of evaluation. The average age and duration of symptoms at the time of evaluation was 45 ± 9.6 years and 3.6 ± 1.06 years, respectively. Three patients were asymptomatic and evaluated because of unexplained cardiomegaly. There were 41 men and 19 women of which 39 were Negro. A total of 19 patients had a long history of a very high intake of alcohol and probably represent alcoholic cardiomyopathy (Table I). Seven patients were classified as having familial cardiomyopathy on the basis of a history of another young member of the family having unexplained cardiomegaly. Four patients were designated as having possible familial cardiomyopathy. Of 11 patients considered to have familial cardiomyopathy, four were chronic alcoholics, making etiological classification difficult. Two patients had a documented history of myocarditis and apparently were left with enlarged hearts. Two patients were classified as having postpartum heart disease; one patient had the onset of symptoms in her sixth month of pregnancy and she died eight months after delivery. The second patient became symptomatic four weeks post partum and died two years later. The remaining 26 patients, even after extensive work-up, had no evidence of a specific etiological basis for their heart disease and, therefore, were designated as idiopathic. The entire group were evaluated together since there was no way to distinguish them other than by history. Cardiac catheterization was performed on 50 patients and included selective coronary angiograms in eight patients. All patients had evidence of some form of myocardial dysfunction, but not one demonstrated any intracardiac shunts or valvular stenosis. Of the entire group of patients, 11 have since died as a direct result of their myocardial disease and postmortem examinations were performed on ten of these patients. Table III gives the age of death, clinical diagnosis, and pertinent postmortem findings in these ten patients.

Standard 12 lead ECG's (1 mv. = 10 mm.) were taken on all of these patients.

Table III. Postmortem findings in ten patients with primary myocardial disease

Patient	Age	Sex	Race	Clinical diagnosis	Heart weight (grams)	Wall thickness (cm)		Valve circumference (cm)	
						L.V.	*R.V.*	*M.V.*	*T.V.*
W. L.	38	M	N	Alcoholic cardiomyopathy	900	1.7	1.3	13	13
L. R.	27	F	N	Postpartum heart disease	1,050	1.2	0.3	10.5	15
L. B.	41	M	N	Idiopathic cardiomyopathy	700	1.7	1.0	12	15
T. A.	42	M	N	Alcoholic cardiomyopathy	900	0.8	0.2	13	12
S. R.	57	M	C	Alcoholic cardiomyopathy	450	1.5	0.3	11	15
L. A.	59	M	N	Idiopathic cardiomyopathy	700	1.6	0.5	11	13
A. B.	42	M	N	Alcoholic cardiomyopathy	600	1.3	0.6	11	14
J. H.	48	M	N	Familial cardiomyopathy	850	1.7	0.8	13	13
K. S.	26	F	C	Postpartum heart disease	465	1.2	0.4	11	13
H. S.	57	F	C	Idiopathic cardiomyopathy	800	N.M.	N.M.	14	14

M, Male; F, female; N, Negro; C, Caucasian; L.V., left ventricle; R.V., right ventricle; M.V., mitral valve; T.V., tricuspid valve; N.M., not measured.

All previous ECG's on prior admissions were reviewed. In some instances ECG's were obtained from other institutions where the patient had previously been admitted. Therefore ECG's were available from the onset of initial symptoms in most cases. Follow-up ECG's were taken in the PMD clinic. A total of 1,140 ECG's were available for review. The ECG's were reviewed with special reference to arrhythmias. The P waves were examined in reference to configuration and duration. Left atrial enlargement was diagnosed if at least two of the following three criteria were fulfilled: (1) a P wave duration equal or greater than 0.12 sec., (2) terminal forces in V_1 equal to or more negative than -0.04 mm. per second[19] (3) Macruz index, i.e., P wave duration per PR segment greater than 1.6 in Lead II.[20] Right atrial enlargement was diagnosed if the amplitude of the P wave was equal to or greater than 2.5 mm. in aVF or the precordial leads or equal or greater than 3 mm. in Leads II and III. Biatrial enlargement was diagnosed if the criteria of both left and right atrial enlargement was satisfied. The mean manifest QRS axis was determined by the method of Grant[21] with the use of Bailey's triaxial reference system. Abnormal left axis was defined if the mean manifest QRS axis was located between -30 and -90 degrees. Left ventricular hypertrophy was diagnosed if the voltage criteria of Sokolow and Lyon[22] were satisfied. If the QRS duration measured 0.12 sec. or more, the diagnosis of left bundle branch or right bundle branch block was made according to previously described criteria.[23] Low voltage of QRS in the standard and unipolar limb leads was defined if the QRS amplitude was equal to or less than 5 mm. Low voltage in the precordial leads was defined if the QRS amplitude was equal to or less than 10 mm. The corrected QT segment was determined from the nomogram derived from Kissin and associates.[24]

Mural thrombi	Emboli	Comments
Right atrium, right ventricle	Pulmonary, renal	Subendocardial and interstitial fibrosis of myocardium normal coronary vessels
None	None	Marked dilatation of all chambers of the heart with localized left ventricular apical fibrosis
None	Spleen	Myocardial hypertrophy with squaring of the nuclei slight intimal proliferation of the small coronary vessels
Left atrium	Pulmonary	Marked hypertrophy and dilatation of both ventricles with focal scarring normal coronary vessels
None	Pulmonary	Hypertrophy and dilatation of both ventricles prominent large nuclei no fibrosis normal coronary vessels
Right atrium	Pulmonary	Myocardial hypertrophy and enlargement of nuclei normal coronary vessels
None	Pulmonary	Endocardial thickening and myocardial hypertrophy and dilatation interstitial fibrosis normal coronary vessels
Left ventricle, right atrium	None	Localized fibrosis of ventricular septum marked diffuse myocardial hypertrophy and fibrosis normal coronary vessels
None	Pulmonary	Focal and diffuse interstitial fibrosis fibrous replacement of myocardium with scar formation
Left atrium	Spleen, renal	Dilatation and hypertrophy of all chambers vacuolation of cytoplasm myoid giant cells with asteroid formation normal coronary vessels

Results

Rhythm disturbance. The basic rhythm in the majority of patients was sinus rhythm (Table IV) Seven patients had persistent sinus tachycardia. Six patients had atrial fibrillation of which one converted to normal sinus rhythm with quinidine. In only 21 patients was normal sinus rhythm maintained without any evidence of rhythm disturbance The remaining 39 patients demonstrated varying degrees of rhythm disturbance (Table IV) In 18 patients, ventricular premature beats were frequent throughout their entire course and usually associated with other evidence of rhythm disturbance. Three of these patients succumbed to ventricular tachycardia or fibrillation

P wave. In 7 patients striking diphasic P waves were noted in Lead VI (Fig 1) A total of 20 patients (37 per cent of the patients in normal sinus rhythm) had criteria for only left atrial enlargement and 14 of these patients also had left atrial enlargement evident on cardiac series. Bilateral enlargement was present in seven patients and right atrial enlargement in one patient.

P R interval A P R interval greater than 0.20 sec. was noted in 11 patients. No patient demonstrated any evidence of pre-excitation or further degree of atrioventricular block.

QRS Low voltage in the standard and unipolar limb leads with normal voltage in the precordial leads was present in 15 patients (Fig 2) and low voltage in all leads was present in one patient. The QRS duration was between 0 07 and 0 09 sec. in 31 patients In the remaining patients, there was prolongation of the QRS duration in 15 patients the QRS duration was 0 10 to 0 11 sec in 8 patients it was 0.12 to 0 14 sec. and in 6 patients the QRS measured between 0 15 and 0 18 sec. Fig 3 shows the distribution of the mean manifest QRS axis as determined from the frontal leads. In 41 7 per cent of the pa

Table IV

Rhythm	*N*		*Per cent*
Sinus		54	90 0
Normal	42		
Bradycardia	2		
Tachycardia	7		
Atrial fibrillation		6	10 0
Rhythm disturbances		39	65 0
Wandering pacemaker	2		3 3
Sinus arrest	2		3 3
Atrial premature beats	5		8 3
Paroxysmal atrial tachycardia	3		5 0
Paroxysmal atrial flutter	1		1 7
Paroxysmal atrial fibrillation	6		10 0
Nodal premature beats	2		3 3
Paroxysmal nodal tachycardia	1		1 7
Ventricular premature beats	31		51 7
Occasional	13		21 7
Frequent	18		30 0
Ventricular bigeminy	4		6 7
Multifocal ventricular premature beats	14		23 3
Ventricular tachycardia	1		1 7
Ventricular fibrillation	2		3 3
No rhythm disturbances		21	35 0

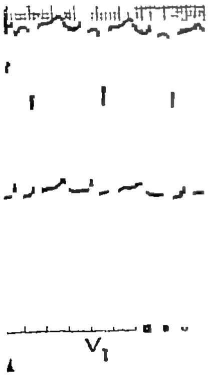

Fig. 1 Typical diphasic P waves as noted in Lead V1 that were observed in 27 patients.

tients, there was abnormal left axis while in 21 7 per cent of the patients, the mean QRS axis was 0° to less than −30° Two patients had right axis deviation. The mean QRS axis for the entire group of 60 patients was −4 ± 51.5 degrees. There were 21 patients with absent Q waves in Leads I aV$_L$ and V$_{5-6}$ with 11 of these patients also having left axis deviation

Table V gives the QRS diagnosis in these 60 patients. Deep S waves in V$_1$ and V suggested left ventricular hypertrophy in eight patients A total of 14 patients were classified as having nondiagnostic abnormalities on the basis of abnormal left axis or a nonspecific intra

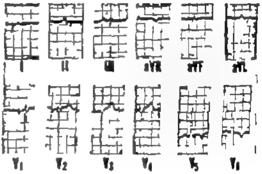

Fig. 2 ECG of D B 36-year-old Caucasian man, demonstrating low voltage in the standard and unipolar limb leads with normal voltage in the precordial leads.

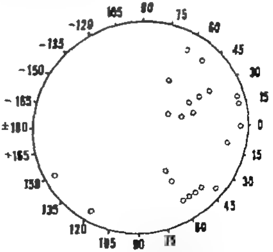

Fig. 3 Distribution of the mean QRS vector in the frontal plane in 60 patients with PMD

ventricular conduction disturbance. Two patients had normal QRS patterns.

The Q-T interval was prolonged in 29 patients. More than half the patients (60 per cent) had depression of the ST segment. Inverted or shallow T waves were present in 80 per cent of the patients. Except for the patients with right bundle branch block, the ST depression and T wave changes were present in Leads I, aVL, and the left precordial leads. The ST segment depression and T wave abnormalities were almost invariably associated with QRS abnormalities and/or digitalis. The two patients with a normal QRS had isoelectric ST segments; one patient had shallow T waves and the other patient had normal T waves.

Abnormal Q waves. In five patients pathological Q waves were noted which suggested previous myocardial infarction (Table VI). None of these patients had any history suggestive of arteriosclerotic heart disease. In three of these patients selective coronary angiograms were performed and revealed normal coronary arteries.

Serial ECG's. Reviewing all available ECG's, significant changes were noted in nine patients (Figs. 4 and 5). Two patients developed abnormal prolongation of the P-R interval. An axis shift to the left and superior was present in six patients. The R waves in the left precordium diminished in six patients, whereas the S waves in the right precordial leads persisted indicating a posterior shift of the electrical axis in the horizontal plane. One patient had decreased QRS voltage in all leads, while another patient developed decreased voltage only in the standard and unipolar limb leads. Four patients have since died and postmortem reports obtained in three of these patients confirmed the clinical diagnosis.

Discussion

These 60 patients represent our limited experience with PMD. The designation of PMD is used to distinguish these patients from other patients who may have myocardial alterations as a result of valvular or coronary artery disease. Furthermore, PMD implies no evidence of hypertension or pericardial disease which in themselves can cause myocardial dysfunction. We have adopted the classification of Harvey and colleagues[13] in grouping these patients in two general types realizing that in some instances the types are arbitrarily defined and need further clarification. These two general types of PMD include (1) idiopathic in which no etiology is clinically apparent and (2) those situations in which an etiologic or clinical spectrum is present associated with evidence of myocardial disease. With further understanding and investigation the idiopathic group may become smaller

Table V

QRS diagnosis	*Total*
Left ventricular hypertrophy	20
Suggestive of left ventricular hypertrophy	8
Left bundle branch block	10
Right bundle branch block	6
Nondiagnostic abnormality	14
Normal	2

Table VI. Abnormal Q waves in ECG

Patient	*Age*	*Race*	*Sex*	*Comments*
R. C.	39	N	[illegible]	QS in V1; familial myocardiopathy
R. D.	38	N	M	QS in V_{1-4}; normal selective coronary angiogram; alcoholic myocardiopathy
J. H.	45	N	M	QS in V_{1-3}; normal selective coronary angiogram; idiopathic myocardiopathy; postmortem heart weight 850 grams and normal coronary arteries
L. J.	39	C	M	"W"-shaped complexes in II, III, and V, with wide deep Q waves in V_{4-6}; normal selective coronary angiogram; idiopathic myocardiopathy
F. M.	36	N	M	QS in V_{1-3}; alcoholic myocardiopathy

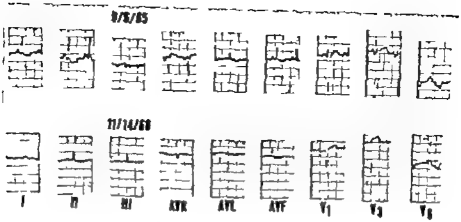

Fig 4 Serial electrocardiographic changes in W D a 39-year-old Negro man, demonstrating loss of frontal plane voltage.

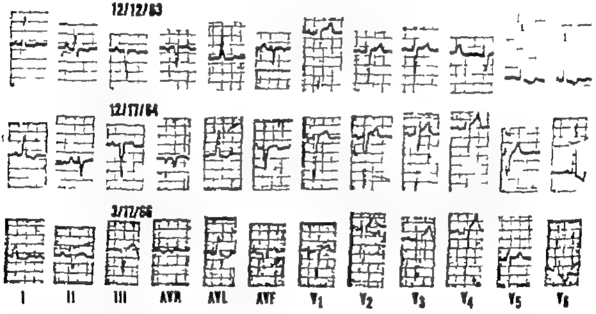

Fig 5 Serial electrocardiographic changes in W L., a 38-year-old Negro man, demonstrating leftward and superior shift of the frontal mean axis. Also note loss of R voltage in the left precordial leads with persistent deep S waves in the right precordium indicating posterior shift in the horizontal plane.

However it is apparent that specific etiologic classification may have to wait until pathological evaluation is available. In our experience thus far the clinical spectrum is the same in the idiopathic familial or alcoholic group. The electrocardiographic evaluation did not permit any separation. Occasionally a specific electrocardiographic pattern in a particular clinical setting can suggest an etiologic diagnosis. In Duchenne's progressive muscular dystrophy a distinctive ECG has been noted that is characterized by tall R waves in the right precordium and deep Q waves in the limb and left precordial leads due to diffuse interstitial fibrosis in the basal portion of the left ventricle.[18] However in hypertrophic subaortic stenosis a similar pattern has been described and attributed to marked septal hyper-

trophy.[37] It is interesting to note that in the former situation the electrocardiographic alterations are due to the subtraction and in the latter due to the addition of electrical forces. In Friedreich's ataxia right axis deviation appears to be frequent but here the etiological diagnosis is clinically apparent.[38,39] Endomyocardial fibrosis apparently has a greater incidence of right ventricular hypertrophy evident on the ECG than any other type of PMD.[30-32]

The basic rhythm in this series of patients was normal sinus rhythm with only 10 per cent having atrial fibrillation. The reported incidence of atrial fibrillation in PMD in any large series varies from 8.5 per cent[5] to 50 per cent although the series reported by Sackner and associates[8] there was no instance of atrial fibrillation. The presence of atrial fibrillation in a patient with an apical pansystolic murmur and an enlarged left atrium may suggest rheumatic heart disease. In one of our patients, this diagnosis was made. The patient underwent cardiac operation and died on the operating table. The only suggestion preoperatively that the diagnosis was incorrect was the absence of valvular calcification and the presence of abnormal left axis deviation. Similar experience has been noted by Alexander. Atrial fibrillation in hypertrophic subaortic stenosis is uncommon.[21,36] Persistent sinus tachycardia was noted in seven of our patients and has been noted by others.[7] In our patients, thyroid work up was negative and cardiac catheterization revealed a low or normal cardiac output and a low stroke volume which suggested that the sinus tachycardia may be a physiological attempt to maintain an adequate cardiac output. In none of our patients was Wolff-Parkinson-White syndrome present its presence being more common in familial myocardiopathy,[34,37-41] less frequent in hypertrophic subaortic stenosis,[23,31] and rarely reported in idiopathic myocardiopathy.[34,41]

Disturbance in rhythm has been a rather striking finding in the present series of cases with only 35 per cent showing no evidence of any rhythm disturbance. Since most of these patients were on digitalis, the question of digitalis toxicity has always been raised. However, even after withdrawing digitalis, the rhythm disturbances persisted. Many patients had evidence of rhythm disturbance when first seen and prior to digitalis therapy. In our experience the rhythm disturbance has been refractory to all modes of therapy. Rhythm disturbances have been noted to be a prominent feature of PMD be it idiopathic[4,7,8,10,21,42] in type or a specific cardiomyopathy such as alcoholic,[19,43,44] progressive muscular dystrophy,[35] Friedreich's ataxia,[9] familial[34,37,45] or amyloidosis.[46]

Abnormally broad and tall as well as notched, P waves in the ECG and especially prominent bifid P waves in Lead V have been conspicuous in PMD[21,36,47] being observed in alcoholic cardiomyopathy,[3,4] familial cardiomyopathy,[34,45,?] and endomyocardial fibrosis[30-32,34] whereas in cardiac amyloidosis the P waves are small.[42] In the present series, 51.9 per cent of the patients in normal sinus rhythm had abnormal P waves suggesting atrial hypertrophy and 50 per cent had prominent bifid P waves present in Lead V. The finding that 70 per cent of those patients with criteria for left atrial hypertrophy also had an enlarged left atrium on roentgenographic evaluation would indicate that these P wave changes are due to atrial enlargement rather than an intra-atrial conduction disturbance.

Atrioventricular and intraventricular conduction defects noted in the present series has been observed by others.[10,2,21,36,47,47] Prolongation of the P-R interval present in 20.4 per cent of the patients in normal sinus rhythm has been reported to vary from 6 to 30 per cent[1,34,47] of patients with PMD. Left bundle branch block was observed in 16.7 per cent while right bundle branch block was noted in 10 per cent of the patients the reported incidence in the literature is between 10 to 21 per cent and 4 to 10 per cent respectively.[31,34] Low voltage in the standard and unipolar limb leads with normal voltage in the precordial lead was also conspicuous being present in 25 per cent of the patients. Similar findings have been commented upon by others.[21,31,36] Although low voltage in the frontal leads is common in cardiac amyloidosis[42,46] low voltage in all the leads appears more

specific.[illegible] Low voltage in all leads may also occur in endomyocardial fibrosis.[illegible] Only one patient in the present series had low voltage in all leads and this was a 42-year-old Negro man with alcoholic myocardiopathy.

Abnormal left axis deviation has been a feature reported by most authors when describing the ECG in PMD.[illegible] In the present series, 41.7 per cent of the patients had this finding. Furthermore, six patients with serial electrocardiographic changes developed an abnormal leftward and superior shift of the mean QRS vector in the frontal plane. The reported incidence of abnormal left axis in idiopathic myocardiopathy has varied from 18[illegible] to 58 per cent.[illegible] The myocardiopathy associated with Friedreich's ataxia appears to be the only one in which right axis deviation is present in a significant number.[24,29] The two patients in the present series with right axis deviation had no evidence of any neurologic disorders; one had a familial cardiomyopathy and the other had an idiopathic cardiomyopathy. Davies and Evans[77] evaluated the incidence of left axis deviation in 200 normal subjects and noted its absence in subjects under 40 years of age whereas left axis deviation was present in three subjects out of 110 over 40 years of age, one of whom had an abnormal exercise ECG. Furthermore, Davies and Evans[77] noted in 200 patients with left axis deviation a 16 per cent incidence of myocardial infarction, almost *invariably anterolateral. However, in* their selected series, the highest incidence of left axis deviation occurred in PMD. The series of Davies and Evans[77] and that reported by Banta and associates[44] included cases of amyloidosis, Friedreich's ataxia, idiopathic and familial myocardiopathy, hemochromatosis, and progressive muscular dystrophy. The highest incidence of abnormal left axis deviation occurred in idiopathic myocardiopathy. Schamroth and Blumsohn[44] studied 756 consecutive cases of left axis deviation in Africans and noted the highest incidence in PMD. Abnormal left axis may also be found in coronary artery disease, aortic stenosis, left ventricular hypertrophy, obesity, or chronic lung disease.[illegible] In the absence of obesity *and chronic lung disease, abnormal left* axis deviation usually indicates some form of left ventricular disorder.[illegible] Pathologically, left axis deviation is associated with myocardial fibrosis[illegible] and does not appear related to the severity of hypertrophy.[illegible] Lev and co-workers[illegible] demonstrated that the left bundle as it appears on the left side of the interventricular septum immediately divides into an inferior and superior division. The superior division distributes fibers superiorly and anteriorly over the subendocardium of the anterolateral wall of the left ventricle. It is generally believed that abnormal left axis results from involvement of this superior division resulting in a terminal vector oriented superior and leftward.[illegible] This is supported by animal experimentation demonstrating that interruption of the anterior fibers of the left bundle in the dog[71] results in some leftward shift of the QRS. However, a similar surgical procedure in the baboon[72] will produce true left axis deviation. The difference of the results in the dog and baboon appears to be on the basis of species characteristics. Furthermore, following an operation for aortic stenosis[73] and hypertrophic subaortic stenosis[illegible] it is not uncommon to find *postoperatively left axis deviation* probably on the basis of damage to the superior group of fibers from the left bundle.

A total of 21 patients (35.0 per cent) had ECG's showing no initial Q waves in Leads I, aVL, and V5-6. Horan and colleagues[illegible] noted this finding in 40 per cent of their patients. The initial Q waves present normally in these leads reflect early depolarization in the mid-portion of the superficial surface of the left side of the septum with early *depolarization* occurring anterior to the right and slightly downward.[77] *According to Burch and* DePasquale[78] the absence of Q wave in Leads I, aVL, and V5-6 reflects septal fibrosis. These authors found absent Q waves in these leads in 80 per cent of their patients with septal fibrosis whereas these Q waves were absent in only 2 per cent of a total of 1,184 autopsies that had no septal fibrosis. It is interesting that of these 21 patients with absent septal Q waves, 11 had abnormal left axis deviation. This suggests that these 11 patients probably have diffuse fibrosis involving not

only the septum but also the anterolateral wall of the left ventricle. Also of note was the finding that the highest incidence of left axis deviation in respect to the QRS diagnosis appeared in the patients with right bundle branch block. In the six patients with right bundle branch block, five patients had abnormal left axis deviation. Two of these patients with left axis deviation and right bundle branch block died suddenly. Unfortunately no autopsies were performed. Here again, this would suggest diffuse fibrosis and possible involvement of the inferior branch of the left bundle resulting in sudden death from complete heart block.

Abnormal Q waves in the ECG were found in 8.3 per cent of the patients. Pathological Q waves have been noted by most authors when describing the ECG of PMD.[2, 13, 18, 21, 22, 23, 27, 28, 32, 33, 73, 77] Pruitt and associates[71] commented on the apical lateral infarction pattern in three patients characterized by prominent Q waves in Leads I, aV$_L$, and V$_{5-6}$ with a pure R wave in aV$_R$. Postmortem examination revealed normal coronary arteries with fibrosis and a thin left ventricular wall. The fibrosis was prominent in the apicolateral wall. The pathological correlation of the Q waves in Duchenne's progressive muscular dystrophy[46] and hypertrophic subaortic stenosis[77] has already been commented on. The Q waves may be noted in any lead but occur more frequently in the right precordial leads.[44, 22, 33, 56] The highest incidence of abnormal Q waves apparently is present in cardiac amyloidosis being reported by Eliot and associates[49] to occur in V$_{1-3}$ in 52 per cent of the cases.

The ST segment depressions noted in these patients were nonspecific and always associated with T-wave changes. The T wave changes observed in the present series were nonspecific and related to digitalis effect or QRS abnormalities. The 19 patients with alcoholic cardiomyopathies had T wave changes in no way different from the entire group. Evans[41] described unique T-wave changes in chronic alcoholics, however, these changes may be altered by digitalis and QRS abnormalities. The specific T waves when noted are usually found in the early phase[1] of alcoholic cardiomyopathy, with more advanced disease the QRS is usually altered resulting in secondary T wave changes.

Serial electrocardiographic changes have been previously commented on by others.[4, 39] Dye and co-workers noted changes reflecting an increasing atrioventricular and intraventricular block. In two patients, there was loss of QRS voltage. Banta and Estes[39] noted abnormal left axis deviation developing in two patients. The observations in the present series are interesting in that they reveal changing electrical axis to the left and superior in six patients and a posterior shift in the horizontal plane as indicated by persistent prominent S waves in the right precordium and diminished R voltage in the left precordium. In eight other patients and electrocardiographic diagnosis was made suggestive of left ventricular hypertrophy because of the presence of only deep S waves in the right precordium. Six of these patients had VCG's which revealed in only one criteria for left ventricular hypertrophy. In the remaining five patients, the vector loop in the horizontal plane was abnormally posterior.

Although the electrocardiographic findings in these patients are nonspecific, we have been impressed by the combination of abnormal P waves and abnormal left axis deviation. This combination was found in 27 per cent of our patients. In any patient under 45 years of age, this combination should alert one to the diagnosis of PMD. Congenital and rheumatic heart disease is easily ruled out by clinical examination. Abnormal P waves and abnormal left axis deviation was found in 52 and 59 per cent of our patients under 45 years of age, while the combination was present in 37 per cent of the patients.

Summary

The electrocardiographic features in 60 patients with primary myocardial disease is presented. The outstanding findings include rhythm disturbances (65 per cent), abnormal P waves (51.9 per cent) and atrioventricular conduction disturbances (20.4 per cent). The QRS abnormalities included low voltage in the standard and unipolar limb leads (25 per cent), right (10 per cent) and left (16.7 per cent) bundle branch block, left ventricular hypertrophy

(46 7 per cent) and abnormal left axis deviation (41 7 per cent) Also noted in the QRS was absent septal Q waves (35 0 per cent) and abnormal Q waves (8.3 per cent) Serial electrocardiographic findings in eight patients were presented which showed a leftward and superior shift of the QRS axis and a decrease in R voltage in the left precordial leads. A review of the literature of the electrocardiographic aspects of PMD is presented

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REFERENCES

1 Blankenhorn, M A nd Gall, E A Myocarditis and myocardosis A clinicopathologic ppraisal, *Circulation 13:217 1956.*
2. Yu, P N Schreiner B F Cohen J and Murphy G W Idiopathic cardiomyopathy A study of left ventricular function and pulmonary circulation in 15 patients, AM. HEART J 71:330, 1966.
3. Alexander C S Idiopathic heart disease. I Anal sis of 100 cases, with special reference to chronic lcoholism, Am J Med. 41:213 1966.
4 Spodick D H and Littmann, D *Idiopathic* myocardial hypertrophy Am J Cardiol. 1:610 1958
5 Evans, B Obscure cardiopathy Brit. Heart J 19 164 1957
6. Higginson J Isaacson C., and Simon, I The pathology of cryptogenic heart disease Arch. Path. 70:497 1960
7 Segal, J P Harvey W P nd Gurel T Diagnosis and treatment of primary myocardial disease, Circulation 32:837 1965.
8 Massumi, R. A Rios, J C., Gooch, A S Nutter D De Vita, V T and D tlow D W Primary myocardial disease Report of fifty cases nd review of the subject, Circulation 31 19 1965
9 Fowler N O and Gueron, M Primary myocardial *disease, Circulation 32:830 1965*
10. Dye C. L. Rosenbaum, D Lowe, J C., Behnke, R. H and Genovese P D : Primary myocardial disease, I Clinical features, Ann. *Int Med. 58:426 1963.*
11 Fowler N O Classification and differential diagnosis of the myocardiopathies, Progr Cardiovas. Dis. 7 1 1964
12. Harvey W P Segal, J P nd Gurel, T : The clinical spectrum of primary myocardial disease Progr Cardiovas. Dis. 7:17 1964
13. Mattingly T W : The clinical concept of *primary myocardial disease*, Circulation 32:845, 1965
14. Evans, W F milial cardiomegaly Brit. Heart J *11:68, 1949*
15. Bra nwald E., Morrow A. G., Cornell W P Aygen M M and Hilbish, T F : Idiopathic hypertrophic subaortic tenosis, clinical, hemodynamic, and angiographic manifestations, Am. J Med. 29:924 1960.
16. Estes, E. H Whalen, R. E. Roberts, S. R J nd McI tosh, H D Th electrocardiographic nd vectorcardiographic findings in idiopathic hypertrophic subaortic stenosis AM. HEART J 63 155 1963
17 Gorli R. The hyperkinetic heart syndrome, J A.M.A. 182:823 1962
18. Evans, W Alcoholic cardiomyopathy AM HEART J *61:556 1961*
19 Brigden W and Robinson J Alcoholic *heart disease, Brit M J 2:1283 1964.*
20. Morris, J J J Estes, E. H, J Whalen R. E., Thompson H K and M Intosh H D P wave analysis i valvular heart disease, Circulation 29:242 1964
21 M crus, R Perloff J K and Case, R. B M thod for the ECG recognition of trial enlargement, Circulation *17:882 1958*
22. Gra t, R P Spatial vector electrocardiography A method for calculating the spatial electrical vectors of the heart from conventional leads, Circulation *11:676 1950*
23. Sokolow M nd Lyon T P The ventricular complex in *left* ventricular hypertroph as obtained by nipolar precordial and limb leads, *AM HEART J 37 161 1949*
24 H wie, E and W ldh T Cli ical vector cardiography nd electroc rdiography Chicago, 1960 The Yea Book Publishers, Inc pp. 226 247
25. Kl**e**in M Schwarzschild, M M and Bak t H A nomogram for rate correction of the Q-T i terval in the electrocardiogram A HEART J *35:990, 1948.*
26. Perloff J K Roberts, W C. de Leon A C J nd O Doherty D The d st nctive elec trocardiogram of Duchenne progressive muscular dystrophy A electrocardiographic-pathologic correlative study Am. J Med 42:179 19'7
27 Braudo, M Wigle E D and Keith, J D Distinctiv electrocardiogram in muscula subaortic *tenosis due t ventricula* septal hypertrophy *Am. J* Cardiol. 14:599 1964
28. Lorenz, T H Kurtz C M and Shapiro, *H M Cardiopathy in Friedreich t xia (spinal form of hereditary sclerosis) Review* of l'terat re nd analy is of cases in five sib*lings*, Arch. I t. Med. 86:412, 1950.
29. Manning G. W : Cardiac manifestations in Friedreich taxia, AM. HEART J 39 799 1950.
30. Shillingford, J P and Somers, K. Clinical and hemodynamic patterns i endomyocardial fibrosis, Brit Heart J 23 433, 1961
31 Williams, A. W., nd Somers, K The electrocardiogram in *endomyocardial fibrosis, Brit.* Heart J 23 311 1960.
32. Abrahams, D G. An usual form *of heart* disease in West Africa: It relation to endomyocardial fibrosis, Lancet 2 111 1959

33 Ball, J D Davies, J N P and Williams, A W Endomyocardial fibrosis, Lancet 1 1049 1954
34 Marriott, H J L Electrocardiographic abnormalities, conduction disorders, and arrhythmias in primary myocardial disease, Progr Cardiovas Dis 7 99 1964
35 Sackner M. A., Lewis, D H Robinson M J and Beflet, S. Idiopathic myocardial hypertrophy Am. J Cardiol. 7 714 1961
36 Hollister R M and Goodwin, J F The electrocardiogram in cardiomyopathy Brit. Heart J 25:357 1963.
37 Harry I Sherl L. and Solomon, M Familial cardiomyopathy With special consideration of electrocardiographic and vectorcardiographic findings, Am J Cardiol 13 734 1964
38. Schiebler G., Adams, P J and Anderson, R. C. Familial cardiomegaly in association with the Wolff Parkinson-White syndrome AM HEART J 58 113, 1959
39 Schrader W H Pankey G A Davis, R B and Theologides, A Familial idiopathic cardiomegaly Circulation 21:599 1961
40 Westlake, R. E., Cohen W and Willis, W H Wolff Parkinson-White syndrome and familial cardiomegaly AM HEART J 61:314 1962
41 Weber D J Gould, L., nd Schaffer A I A family with idiopathic myocardial hypertrophy Am J Cardiol 1 419 1966
42. Braunwald, E., nd A gen, M M Idiopathic myocardial hypertrophy without congestive heart failure or obstruction to blood flow Clinical hemodynamic, and angiocardiographic studies in fourteen patients, Am J Med 35 7 1963
43. Barritt, D W nd Al-Shamma a, M Heart failure with unexplained cardiomyopathy Brit. Heart J 28:674 1966
44 Evans, W The electrocardiogram of alcoholic cardiomyopathy Brit. Heart J 21:445 1959
45 Brigden, W Uncommon myocardial diseases The non-coronary cardiomyopathies, Lancet 2:1243 1957
46. Eliot, R S McGee H J and Blount, S G Cardiac amyloidosis, Circulation 23:613 1961
47 Brigden, W Uncommon myocardial diseases, the non-coronary cardiomyopathies, Lancet 2:1179 1957
48 Barry M and Hall, M F milial cardiomyopathy Brit Heart J 21:613 1962
49 Whitfield, A. G. W Familial cardiomyopathy Quart. J Med. 30 119 1961
50. Abrahams, G D Endomyocardial fibrosis of the right ventricle, Quart J Med 31:1 1962.
51 Brigden, W Cardiac amyloidosis, Progr Cardiovas Dis 142, 1964
52. Correa, P Restrepo, C Garcia C and Quiroz, A C. P hology of heart disease of undetermined etiology hich occur in Cali, Columbia, AM. HEART J 66:584 1963
53 Farrokh A., Walsh, T J and Massie, E. Amyloid heart disease, Am J Cardiol 13 750, 1964
54 Berenreiter M Cardiac amyloidosis lectrocardiographic findings, Am J Cardiol 1:644 1958
55 Findley J W J and Adams, W Primary systemic amyloidosis stimulating constrictive pericarditis with steatorrhea and hyperesthesia, Arch Int. Med. 81:342, 1948
56. Banta H D Greenfield, J C J and Estes, E H J Left axis deviation Am J Cardiol. 14:330, 1964
57 Davies, H and Evans, W The significance of a deep S ve in Leads II nd III of the electrocardiogram Brit Heart J 22:551 1960
58. Josselson, A J and Pruitt, R. D Electrocardiographic findings in cardiac amyloidosis, Circulation 7:200, 1953.
59 Bradlow B. A Zion, M M and Fleishman S. J Heart disease in Africa, with particular reference to southern Africa, Am. J Cardiol. 13:650 1964
60. Schamroth, L and Blumsohn, D The significance of left axis deviation in heart disease of the Africans. Brit Heart J 23:405 1961
61 Corne, R A., Parkin, T W Brandenburg R O and Brown, A L Significance of marked left axis deviation. Electrocardiographic-pathologic correlative study Am J Cardiol 15:605 1965
62 Castle C H and Keane W M Electrocardiographic Peri-Infarction Block A clinical and pathologic correlation Circulation 31:403 1965
63 Curd, G W J Hicks, W M J and Gyorkey F Marked left axis deviation Indication of cardiac abnormality AM. HEART J 62:462 1961
64 Grant, R P Left axis deviation An electrocardiographic-pathologic correlation study Circulation 14:233 1956
65 O Reilly R. A and Sokolow M Left ventricular conduction defects and left axis deviation in 4 000 consecutive electrocardiograms, Clin Res 11:98, 1963 (abstr)
66 Pryor R and Blount S G J The clinical significance of true left axis deviation Left intraventricular blocks, AM HEART J 72:391 1966
67 Grant, R P Left axis deviation, Mod Conc. Cardiovas. Dis 27:437 1958
68 Widran, J and Lev M The dissection of the atrioventricular node bundle and bundle branches in the human heart Circulation 4:863, 1951
69 Lev M Widran, J and Erickson E E A method for the histopathologic study of the atrioventricular node bundle and branches, Arch Path. 52 73 1951
70. Grant, R P Peri-infarction block Progr Cardiovas Dis 2:237 1959
71 Watt, T B J and Pruitt, R D Electrocardiographic findings associated with experimental arborization block in dogs, AM HEART J 69:642, 1965
72. Watt T B J Murao, S. and Pruitt R. D Left axis deviation induced experimentally in primate heart, AM HEART J 70:381 1965
73 Samson, W F and Bruce, R. A. Left ventricular parietal block produced by transventricular aortic commissurotomy AM HEART J 63:41 1962

74. Sousa, J. E. M. R., de Jesus Zerbini, E., Jatene, A. D., Fontes, V. F., Magalhaes, H. M., and Filho, C. M. C.: Transaortic infundibulectomy for hypertrophic subaortic stenosis, Am. J. Cardiol. 15:801, 1965.
75. Wigle, E. D., Chrysohou, A., and Bigelow, W. G.: Results of ventriculomyotomy in muscular subaortic stenosis, Am. J. Cardiol. 11:572, 1963.
76. Horan, L. G., Flowers, N. C., Thomas, J. R., and Tolleson, W. J.: The spatial vectorcardiogram in idiopathic cardiomyopathy, Progr. Cardiovas. Dis. 7:115, 1964.
77. Sodi Pollares, D., Brancato, R. W., Pileggi, F., Medrano, G. A., Bisteni, A., and Barbato, E.: The ventricular activation and vector cardiographic curve, Am. Heart J. 54:498, 1957.
78. Burch, G., and DePasquale, N.: A study at autopsy of the relation of absence of the Q wave in Leads I, aVL, V5, and V6 to septal fibrosis, Am. Heart J. 60:336, 1960.
79. Pruitt, R. D., Curd, G. W., Jr., and Leachman, R.: Simulation of electrocardiogram of apicolateral myocardial infarction by myocardial destructive lesions of obscure etiology (myocardiopathy), Circulation 25:506, 1962.
80. Bahl, H. D., and Estes, E. H., Jr.: Electrocardiographic and vectorcardiographic findings in patients with idiopathic myocardial hypertrophy, Am. J. Cardiol. 14:218, 1964.

Cardiomyopathies produced by Toxoplasma gondii

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Toxoplasma gondii a parasitic agent, can produce lesions in the brain eyes, uterus, myocardium lymph glands etc. in adults, children and fetus.[1-8] Toxoplasmic etiology of cardiomyopathies has not been investigated as thoroughly as other causes of cardiac involvement. We and others have been studying this parasitic etiology of cardiomyopathies during the last 6 years.[9-11] This report includes 11 patients in which Toxoplasma gondii seems to be the most probable etiology. In 3 of these patients there were evidences of severe myocardium involvement as shown by necropsy and in one of them a parasite was found in the myocardium.

Material and method

Since March, 1960 through April 1966 every patient suffering from a myocardiopathy was investigated as follows history and physical examination nutritional habits, alcoholic ingestion electrocardiogram (ECG) chest x-rays with heart volume calculated by Rohrer and Kahlstorf method[12] phonocardiogram serologic test for syphilis, toxoplasmic infection and Chagas disease electrophoresis of plasma proteins, antistreptolysins titer investigation of lupus erythematosus disseminatus cells, and all the routine laboratory tests (blood cell count urine, glycemia, and uremia) Furthermore vectorcardiograms (VCG) according to Grishmann's cubic system was performed in 10 patients and heart catheterization in 5 Cardiomyopathy diagnosis was made whenever any manifestation of heart disease with or without cardiac enlargement or heart failure was found in patients in which atherosclerosis hypertension syphilis, rheumatic heart disease, cor pulmonale, congenital heart disease, or other known etiologies were ruled out.[13] Toxoplasmic etiology was accepted only when titers of 1/64 of Sabin and Feldman and/or hemagglutination (HAT) reactions increased and complement fixation test (C F T) was positive in any moment during the course of the illness[1-4] Sabin and Feldman and HAT reaction within a range of 1/64 with negative C F T are considered normal in our country Serologic tests are considered highly specific for toxoplasmic infection according to Thiermann and Knierim[4-17] and to our own experience as described below

Our case material comprises 2 groups of patients the first group with heart failure and the second group without. In the first group we had 3 men and 2 women with an

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age distribution ranging from 30 to 49 years. In the second group there were 3 men and 3 women whose ages ranged from 14 to 49 (only 1 woman was 49 the other patients ranged from 14 to 25)

Specific treatment was performed 13 times in 11 patients with 50 mg of pyrimethamine (Daraprim) 1 gram of sulfamethoxypyridazine and 1 mg per kilogram of weight of prednisone during the first 10 days in the following 10 days, half of the doses of pyrimethamine and sulfamethoxypyridazine were used and prednisone was given in progressively decreasing doses. Case 4 received a second treatment when she showed a serologic reactivation The same was done with Case 6 when a choroiditis appeared coincident with serologic reactivation 3 years after the first treatment. In a pregnant woman (Case 1) no prednisone was given and a mixture of sulfadiazine, sulfamerazine, and sulfamethazine was administered in doses of 3 grams for the first 10 days and 2 grams for the second 10 days. In the patients with heart failure, we did not administer digitalis or diuretic in order to assess the effectiveness of the treatment described

An epidemiologic investigation was performed in all patients. This included a serologic study of the persons living with the patient and a history of contacts with domestic animals such as chickens, cats, and dogs. In Case 5 an experimental inoculation of a macerate of an axillary gland was performed in mice. Necropsies were carried out in the cases of the 3 patients who died Histologic study was thoroughly done. Multiple blocks were obtained and studied in serial sections. *In 2 of*

Table 1 Patients without heart failure

Case	*Age*	*Sex*	*Symptoms before admission*	*Complication*	*Results*
1	19	F	3 mo. precordial pains, palpitations obstetrical problems 1 child with congenital disease died at delivery	None	Good clinical improvement cardiac complaints disappeared she had 2 pregnancies without complications RBBB persisted
2	17	M	5 mo. palpitation and precordial oppression	Multiple pulmonary emboli	Had died 50 days fter dmission ECG showed progressi myocardial damage Toxoplasma recovered from myocardium by experimental innoculation
3	23	F	1 mo. palpitations and precordial pains sister of Case 2	None	Excellent complaints disappeared ECG became normal heart size became normal no limitations 3 years after admission
4	49	F	5 yr palpitations and shortness of breath	None	Excellent symptoms disappeared ECG became normal heart size decreased symptom-free 3 ears fter treatment serologic reactivation treated
5	14	M	1 mo. palpitations and dyspnea on great efforts	Generalized toxoplasmosis maculopapular exanthema lymphadenopathy fever innoculation of a macerate of an axillary gland in mice gave positive reactions but parasite not recovered	Excellent symptom-free 3 years fter treatment ECG thout alterations heart size became normal no limitations on effort
6	25	M	4 mo palpitation and precordial pains dyspnea on effort	Gastrointestinal bleeding bilateral choroiditis 3 years after heart involvement with serologic reactivation	Good shortness of breath persisted palpitations disappeared ECG normal after 5 months of treatment serologic reactivation nd choroiditis treated ith excellent results

these patients, experimental innoculations of a macerate of cardiac tissues in mice were done. In Case 2 innoculation with macerate of a mediastinal gland and spleen was also performed Mice were observed for periods ranging from 40 to 120 days during which time serologic reactions were repeatedly performed (Sabin and Feldmann and C F T)

Results

Clinical picture The clinical picture, electrocardiographic and radiologic findings are summarized in Tables I II III and IV Five patients were admitted with symptoms of heart failure Palpitations and/or precordial pain were the only symptoms in 6 patients in all of these patients there were arrhythmias or alterations of the repolarization in the ECG and enlargement of one or more cavities as shown by x-rays. The symptoms were present 1 month to 3 years before admission. It is interesting to note that patients with heart failure in general had symptoms for a longer period of time than those without heart failure. In patients without heart failure complaints had been present for periods of less than 6 months except in the case of one patient in whom symptoms had appeared 1 year before admission. The shortest symptomatic period in the patients with heart failure was 8 months (Case 11) but the other 4 had symptoms for at least 1 year before admission

The physical examination only showed signs related to heart failure or arrhythmias. In one patient there was gland enlargement as a manifestation of a generalized toxoplasmosis (Case 5) Hepatomegaly was only present in patients with congestive heart failure. A short systolic murmur in different areas was the most common finding in auscultation and phonocardiography In Case 8 a holosystolic murmur of the mitral area was heard and inscribed but it disappeared after treatment (Fig 1) In another case an early diastolic murmur

Table II Electrocardiographic and radiologic findings in patients without heart failure*

Case	Electrocardiogram	Radiology
1	A V block 2:1 complete RBBB	Heart volume+† LA + LV + RV + PA dilated
2	Ventricular premature beats; A V block (P R 0 24) subendocardiac damage incomplete LBBB	Heart volume + LA + to ++ RV ++ PA dilated Ao. dilated
3	ST T changes inverted T waves in D and V	Heart volume 0 to + LA ++
4	Bigeminy ST T changes	Heart volume ++ LV +++
5	A-V block 2 1 incomplete LBBB ventricular premature beats left ventricle anterior wall ischemia	Heart volume + LA + LV ++ RV +++
6	ST T changes LVH	Heart volume + RA ++ RV normal LV ++

*Abbreviations RBBB, right bundle branch block; LBBB, left bundle branch block, RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy BVH, biventricular hypertrophy; LA, left atrium, LV left ventricle; RV right ventricle; RA, right atrium; PA, pulmonary artery and Ao, aorta.

†Size of cavities between and 4 + + slight (means double heart volume as expected for body weight and height); ++ moderate (means triple heart volume as expected for body weight and height) +++ marked and ++++ very marked.

Table III Patients with heart failure

Case	*Age*	*Sex*	*Symptoms before admission*	*Complication*	*Result*
7	49	M	2 yr symptoms of left ventricular failure	None	Good symptoms disappeared ischemic T waves and ventricular premature beats disappeared heart size reduced 30% without digitalis for 3 years after discharge
8	30	M	1 yr symptoms of left ventricular failure	None	Excellent symptom-free 2 years after treatment ECG normal heart size decreased
9	44	F	3 yr congestive heart failure	None	Fair transient clinical improvement under control for 2 years with diuretics no digitalis heart size unchanged
10	44	F	3 yr congestive heart failure	None	Bad transient clinical improvement premature beats disappeared heart size augmented died suddenly 6 months after treatment
11	43	M	8 mo congestive heart failure	None	Bad progressive deterioration ECG showed progressive left bundle block died 1 month after admission

Table IV Electrocardiographic and radiologic findings in patients with heart failure*

Case	*Electrocardiogram*	*Radiology*
7	Ventricular premature beats incomplete LBB left ventricle lateral ischemia LVH	Heart volume +++ RA + RV ++ LA ++ to +++ LV +++
8	AV block (P R 0 24) ST T changes left atrium hypertrophy BVH	Heart volume +++ RA ++ RV normal LV ++
9	Bigeminy AV block (P R 0 26) incomplete LBBB LAH BVH	Heart volume +++ RA ++ RV +++ LA +++ to ++++ LV +++ PA dilated Ao dilated
10	Electric alternance multiple ventricular and supraventricular premature beats LVH P wave alterations	Heart volume +++ RA +++ RV ++ LA + LV +++
11	Atrial fibrillation complete LBBB	Heart volume ++++ RA ++ LA +++ to ++++ PA dilated Ao dilated

*Abbreviations as in Table II.

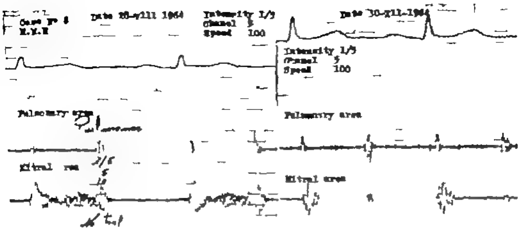

Fig 1 Phonocardiograms recorded before and after treatment. Pansystolic murmur of the mitral area disappeared. Both tracings were registered with the same technique (Case 8)

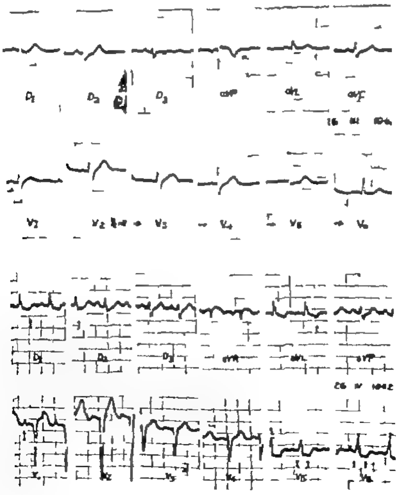

Fig 2. First tracing when admitted, shows slight alterations of ST T segment in D D and V Second tracing shows alterations of ST T segment suggestive of left ventricle subendocardial injury retarded A V conduction, changes in P waves (arrow in V) and disappearance of R in V and V (Case 2).

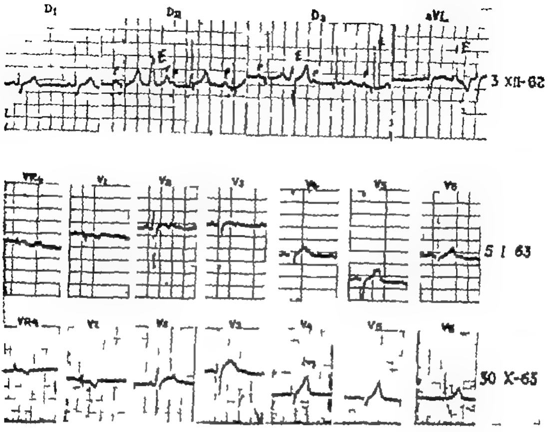

Fig. 3. First tracing before treatment shows A V block of 2 1 type. Second tracing, after treatment, shows normalization of A V block, but alterations of T of ischemic type in V which became normal in third tracing (Case 5).

along the left parasternal border was inscribed (Case 2). This is an unusual finding in patients with primary myocardial disease.[23] In this case Toxoplasma gondii was recovered from myocardium and necrotic lesions were found in the ascending aorta. In 9 patients there were arrhythmias 1 had atrial fibrillation 6 supraventricular premature beats, 1 atrioventricular (A V) block 2 1 associated to ventricular premature beats and 1 A V block 2 1. A prolonged P R interval was present in 3 patients. In 2 of them it was associated with ventricular premature beats. There was a bundle branch block of the right side in 1 and of the left side in 5 patients (Cases 2 3 5 7 9 and 11). In 6 patients, there were electrocardiographic tracings suggestive of myocardial damage or ischemias (Cases 2 3 4 5 6, and 8) 4 of them were young patients 14- 17 23- and 25-years-old (Figs. 2 and 3) and in 1 who died (17 years-old Case 2) necropsy did not show coronary artery disease.

VCG's in 10 patients showed no differences with ECG tracings except in 1 case (Case 6) in which the VCG showed an incomplete right bundle branch block (RBBB) that the ECG failed to show.

The x-rays showed enlargement in all patients. In 2 there was enlargement of only 1 cavity the left atrium in one (Case 3) and the left ventricle in the other (Case 4). Even the patients without heart failure had moderate to important cardiac enlargement. In Cases 3 4 and 5 without heart failure heart size became normal after treatment, and in Cases 7 and 8 with heart failure, a significant reduction of heart size was observed.

In 5 patients, a right heart catheterization was performed. In 3 of the patients in whom the procedure was performed when there was no clinical failure (Cases 3 5 and

Table V Range of titers of serologic reactions before and after treatment

Case	Sabin and Feldman	Hemagglutination	Complement fixation test
1	B 1/64-1/1,024	1/64-1/512	(−)-1/5
	A 1/1,000-1/64	1/512 1/64	1/5-(−)
2	B 1/256	1/512	(−)-1/5
	A 1/256	1/512	1/5
3	B 1/64-1/256	1/64-1/512	(−)-1/5
	A 1/256-1/64	1/512 1/64	1/5-(−)
4	B 1/64-1/256	1/64-1/512	(−)-1/5
	A 1/256	1/512	(−)-1/5-(−)
5	B 1/512	1/512 1/2,000	1/20-1/80
	A 1/512-1/256	1/2,000-1/64	1/80-(−)
6	B 1/256-1/512	1/256-1/512	1/10-1/80
	A 1/51 1/256	1/512 1/256	1/80-1/5
7	B 1/16-1/256	1/64-1/512	(−)-1/5
	A 1/256	1/512 1/64	1/5-(−)
8	B 1/16-1/64	1/256	(−)-1/5
	A 1/64-1/16	1/256-1/64	1/5-(−)
9	B 1/4,000	1/8 000	1/20
	A 1/5,000	1/8,000-1/256	1/20-(−)
10	B 1/16-1/256	1/64-1/512	(−)-1/5
	A 1/256-1/64	1/512 1/256	1/5-(−)
11	B 1/64	1/64-1/256	(−)-1/5
	A 1/64	1/256	1/5

8) cardiac index and pulmonary resistances were normal. In Case 3 in which a left atrial enlargement by x rays was found a transeptal catheterization of the left atrium revealed a normal pressure and the calculated mitral area according to Gorlin's formula was normal (4 sq cm.) In 1 patient with clinical failure (Case 7) there was a low cardiac index, high vascular resistance, and an increase in arteriovenous oxygen difference. In all of the patients, there was a slight elevation of right atrial pressure (mean 5 to 12 mm. Hg)

The serologic study is shown in Table V All the patients had titers which were considered significant for diagnosing toxoplasmic infection, and all of them also presented a positive complement fixation test which indicated actual activity of the disease. The epidemiologic investigation demonstrated direct contact with domestic animals such as dogs, cats, and chickens in 10 patients. A total of 12 relatives were studied. There was active serologic infection in 1 brother and a sister of Case 2 who died and from which Toxoplasma gondii was recovered from the myocardium. The sister is included in this report (Case 3) The brother refused further studies, even though he had cardiac enlargement dyspnea on effort, and palpitations.

Results of treatment Details are given in Tables I and III Among the 6 patients who were admitted without heart failure, one died as a result of pulmonary emboli and acute cor pulmonale (Case 2) In the other 5 the results of treatment were excellent because symptoms disappeared in all but 1 patient (Case 6) heart size became normal or decreased significantly and the arrhythmias or electrocardiographic pattern of ischemia improved or disappeared One of these 5 patients was followed up for 2 years, and the other 4 for periods of 3 years. Two of them (Cases 4 and 6) had a serologic reactivation without signs of new cardiac involvement. In Case 6 this serologic reactivation coincided with bilateral chorioditis This complication subsided after a second treatment. None of them showed recurring symptoms. Case 5 presented signs of generalized acute toxoplasmosis at the time when he was admitted maculopapular exanthema adenopathy fever and general malaise. Experimental innoculation of an axillary gland macerate in mice gave positive serologic reactions but the parasite was not recovered Symptoms disappeared after treatment.

Two of the 5 patients with heart failure died (Cases 10 and 11) In one of them (Case 10) in spite of clinical improvement, x-rays showed an increase of heart size and she died suddenly 6 months after treatment was finished The other patient died in refractory insufficiency 1 month after treatment. The ECG showed progressive left bundle branch block (LBBB) Three patients with heart failure (Cases 7 8, and 9) showed a marked clinical improvement without the use of digitalis, and they have been compensated for periods of 2 to 5 years.

Only 1 patient (Case 6) showed secondary reaction to treatment. He had a gastrointestinal bleeding which subsided with the interruption of prednisone.

Pathology The 2 patients who died in cardiac insufficiency showed marked enlargement of all cavities. One patient (Case 11) had a cardiac weight of 650 grams with marked hypertrophy and dilatation of all

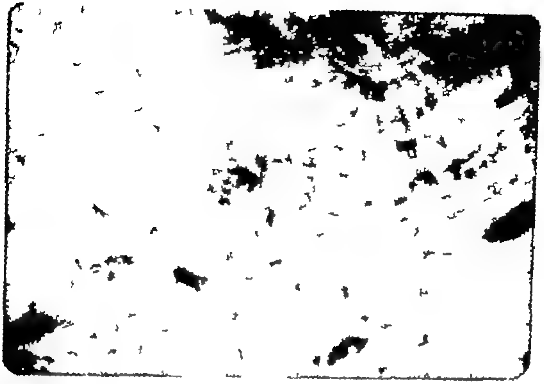

Fig. 4 Histologic section of myocardium showing a pseudoc[illegible]t of Toxoplasma gondi[illegible] Macrophotograph taken with immersion lens (100/1 30 Case 2)

Fig. 5 Histologic section of [illegible]scending aorta taken [illegible]ith minor magn[illegible]fication (10/0 25) [illegible] show the 3 layers. There are 2 necrotic focuses surrounded by polynuclear infiltr[illegible]te There is marked d[illegible]truction of the media but also of the other 2 layers Toxoplasma [illegible] not recovered from this part but necrotic lesion[illegible] [illegible]re simil[illegible] to those produced by th[illegible] parasite (Case [illegible]).

cavities especially of the left ventricle. Microscopic study in this patient revealed extensive fibrosis in both ventricles mainly in the interventricular septum. Inflammatory infiltration was not found. The coronary arteries were thoroughly studied but did not show signs of atherosclerosis. There was valvular indemnity. Experimental inoculation of myocardial tissue in mice was performed but Toxoplasma was not recovered after 120 days of observation.

One patient (Case 10) died in the street and an autopsy was performed at the city morgue. As in Case 11, there was a marked enlargement and hypertrophy of myocardium with extensive fibrotic scars but coronary atheroma or valvular damage were not found.

In Case 2, Toxoplasma gondii was recovered from the myocardium. A complete report of this case has already been made.[9] The parasite was found in the form of pseudocysts in the myocardium (Fig. 4). The ascending aorta showed inflammation involving the 3 layers (Fig. 5). Experimental innoculation in mice was successful. Toxoplasma gondii was recovered after 51 days. Mice which were innoculated with a macerate of the spleen showed positive Sabin and Feldman reaction with titers of 1/2 000 and C.F.T. of 1/4 000. Those innoculated with macerate of a mediastinal lymph node showed no reaction.

Discussion

There is little doubt that in these patients Toxoplasma gondii infection was almost certainly the etiology of heart disease. We have demonstrated the presence of the parasite in the myocardium in 1 of the patients (Case 2). A second patient had a bilateral choroiditis 3 years after heart involvement (Case 6). This patient had prolonged fever of unknown etiology at the age of 14 with adenopathy which subsided spontaneously. In a third patient (Case 5) mice innoculated with a macerate of an axillary gland showed positive serologic reactions. Although it is impossible to rule out other etiologies of cardiac involvement in the rest of the patients, the most common causes of heart disease were not present and the serologic study was diagnostic of Toxoplasma. [27] In our patients the titers were higher than those of the general population which were found to be no higher than 1/64.[19] Furthermore serologic reactions were performed in 112 patients with heart disease of different etiologies. We found only 2 patients in which the titers were higher than 1/64. One of these patients had constrictive pericarditis and the other a rheumatic mitral regurgitation. The titers for HAT were 1:1 024 and 1/4 000 respectively, with positive C.F.T. We believe this patient had active toxoplasmosis. In the other 110 patients, the titers were negative or their maximal value was not higher than 1:64. We considered rising titers and positive C.F.T. which showed activity of the disease to be significant.[6,4] As has been observed by others,[2] C.F.T. became negative shortly after treatment. The epidemiologic study was highly important because it demonstrated a very high incidence of contact with animals which have been considered as carriers of Toxoplasma gondii[28] and permitted us to discover a cardiac compromise in a very early stage in a relative of 1 of the patients (Case 2). The serologic study and the electrocardiographic alterations were the most important diagnostic elements in all the patients. It is important to note that the ECG fluctuates and must, therefore, be repeated periodically.

It is noteworthy that most of the patients were under 40 years of age, an age group in which atherosclerotic heart disease is very uncommon in Chile. This is important if we consider the electrocardiographic tracings showing patterns of ischemia or subendocardiac damage even in patients who were well under 30 years of age.

It seems reasonable to separate patients into 2 distinct groups: one without heart failure which had the shortest history before admission and a second one which presented cardiac failure and had the longest history of complaints. The first group showed a marked improvement after treatment not only of the clinical picture but also of the ECG and heart size. We considered the results of treatment in this group as good or excellent in most of them. Although the complaints were vague and nonspecific, cardiac involvement was conclusively demonstrated by alterations of ECG and x-rays. All the patients showed enlargement of one or more cavities from slight to moderate.

This coincides with Paulley and co-workers[3,4] findings.

Treatment was more effective in the group of patients with left ventricular failure than in those with congestive heart failure. This group showed the greatest cardiac enlargement at x rays.

It has been thought that a specific strain of Toxoplasma might be responsible for the cardiac involvement.[3] Case 5 however would suggest the opposite because he presented myocardial involvement simultaneously with fever, maculopapular exanthema, and lymphadenopathy which have been described in acute toxoplasmosis in adults.[3] We would consider this case as a miliary form according to Theologides classification.[21] Experimental innoculation of a lymph node from this boy gave highly suspicious results because mice presented very high titers of HAT although Toxoplasma was not recovered. Case 6 is another example of different localization of the parasite in the same patient. These facts lead us to think that in some patients cardiac compromise could be the only or the most prominent manifestation of a generalized disease. This was analyzed by Bengtsson.[22]

Hemodynamic findings in 5 of our patients showed no remarkable or specific feature and the procedure was of no risk at all.

We have not seen Stokes-Adams crisis in our patients as found by Shee,[23] although in 2 patients there was A-V block of the 2:1 type. The most frequent arrhythmia was the supraventricular premature beats.

Treatment was made with an association of prednisone with the drugs commonly used (pyrimethamine and sulfadrugs).[2,4] Results were satisfactory in those patients without heart failure and only fair or poor in those with heart failure. We used prednisone because it has been effective in bundle branch and A-V blocks[24] and because the necrotic lesion of Toxoplasma is most probably an autoimmune phenomenon[4] and corticosteroids might control it and prevent later fibrosis. It might be of great value to initiate treatment early in the evolution of the disease. This is exemplified by Case 3. She was a sister of Case 2 and when she came for a routine epidemiologic checkup she had a Sabin and Feldman reaction of 1/64 but C.F.T. was negative. She had no cardiac limitations or complaints and the ECG and chest x rays were normal. After a period of 2 months, she complained of palpitations and precordial pains. The ECG showed alterations of repolarization and there appeared to be left atrial enlargement on the x rays. The serologic study showed Sabin and Feldmann reaction of 1/256, HAT 1/512, and positive C.F.T. 1/5. Symptoms disappeared immediately after treatment was started and ECG and x rays went back to normal. The serologic evolution showed slow regression to normal as in other cases. Her case was followed-up for a period of 3 years during which she had no further complaints.

Pathologic findings in the myocardium have been described as focal necrosis[3,16,17] with lymphocytes, plasma cells, and histiocytic infiltration leading to fibrosis. In one of our patients (Case 2) we found focal necrosis of the 3 layers of the ascending aorta and Toxoplasma was recovered from the myocardium. This focal necrosis of the aorta is most likely of Toxoplasma origin. In the other patients there was only fibrosis. One of them (Case 11) had marked septal fibrosis which would explain the ECG findings of progressive LBBB.

Summary

Eleven cases of cardiomyopathy are presented in which the toxoplasmic infection was ascertained by serologic study. The parasite was recovered from the heart in one of them. All other common etiologies were ruled out by clinical and laboratory procedures.

Results showed 2 different groups of patients: one without and one with cardiac failure. One patient of the first group died as a consequence of pulmonary embolism and in another, cardiac involvement was part of a generalized acute toxoplasmosis. Two patients of the second group died in refractory insufficiency.

Treatment results were generally good. This study suggests that failure might be due to a late complication of the toxoplasmic infection of the heart and that it is most important that proper diagnosis be made as early as possible.

We wish to express our gratitude to the Department of Parasitology (University of Chile), especially

to Dr Guillermo Niedmann and Miss Erika Thiermann for performing the serologic and parasitologic studies, and to Dr Jaime Saavedra for the radiologic study

REFERENCES

1. Apt, W Transmisión congénita. Estado actual del problema. I. Introducción y generalidades, Bol. Chile Parasit. 19:31 1964.
2. Kean, B. H and Breslau, R. C. Parasites of the human heart, New York, 1964, Grune & Stratton, Inc.
3. Paulley J W Jones, R., Green, W P D and Kane, E. P Myocardial toxoplasmosis, Brit. Heart J 18:55 1956.
4. Paulley J W Jones, R., Green, W P D and Kane, E. P Myocardial toxoplasmosis, Lancet 2:624 1954.
5. Tomlinson, W J Human chronic toxoplasmosis, Am. J Clin. Path. 15 123, 1945.
6. Niedmann, G., Thiermann, E., and Neghme, A. Toxoplasmosis en Chile. Estado actual de los estudios clínicos y epidemiológicos, Bol. Chile. Parasit. 18:86, 1963
7. Niedmann, G., Thiermann, E., and Del Campo, E. Un caso de miocarditis crónica toxoplasmica, Bol. Chile. Parasit. 14:59 1959
8. Niedmann, G., Del Campo, E., Thiermann, E., Sánchez, J and Levy M. Myocarditis of probable toxoplasmosis etiologies, Bol. Chile. Parasit. 17:58, 1962.
9. Escobar E., and Arribada, A. Myocardiopathy Some of its possible etiologies, Rev Med. Chile. 89:669 1961
10. Vukasovic, J Arribada, A., Niedmann, G., and Thiermann, E. Myocardiopathy caused by Toxoplasma gondii, Bol. Chile. Parasit. 18:40, 1963.
11. Niedmann, G., Thiermann, E., and Pichard, R.: Nuevo caso de miocardiopatía por Toxoplasma gondii, con demostración parasitológica mediante inoculación experimental, Bol. Chile. Parasit. 19:37 1964.
12. Kjellberg, S. R., Lind, J Lonroth, H. and Rudhe, U Variations in heart volume in normal children of school age, Acta radiol. 41:441 1954.
13. Harvey W P Segal, J P and Gurel, T The clinical spectrum of primary myocardial disease, Progr Cardiovas. Dis. 7:17 1964.
14. Knierim, F El valor de las reacciones serológicas en el diagnóstico de algunas infecciones parasitarias, Bol. Chile. Parasit. 19 119 1964.
15. Thiermann, E., and Naquira, F : Contribución al estudio serológico de la Toxoplasmosis. I. Reacción de Sabin & Feldman y fijación del complemento para la toxoplasmosis muestras de sangre de adultos aparentemente sanos, Bol. Chile. Parasit. 13:26, 1958.
16. Thiermann, E., Apt, W and Niedmann, G. El diagnóstico de laboratorio de la toxoplasmosis, Bol. Chile. Parasit. 21:82, 1966.
17. Thiermann, E., Knierim, F and Niedmann, G. Comparative study of the Sabin-Feldman reaction and hemagglutination test in infections with Toxoplasma gondii, Bol. Chile. Parasit. 18:36, 1963
18. Massumi, R. A., Rios, J C., Gooch, A. S., Nutter D De Vito, V T and Datlow D N Primary myocardial disease report of 50 cases and review of the subject, Circulation 31 19 1965.
19. Cathie, I. A. B. Myocardial toxoplasmosis, Lancet 1 149 1955
20. Alcaino, H Toxoplasmosis en animales domésticos, Bol. Chile. Parasit. 19:21 1964.
21. Theologides, A and Kennedy B J Clinical manifestations of toxoplasmosis in the adult, Arch. Int. Med. 117:536, 1966.
22. Bengtsson, E. Herzaffektion bei Toxoplasmosis, Cardiologia 17:289 1950.
23. Shee, J C. Stokes-Adams attacks due to toxoplasma myocarditis, Brit. Heart J 26 151 1964.

Enzyme changes following direct current countershock

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Direct current (D.C.) countershock is widely used in the conversion of arrhythmias especially atrial fibrillation to sinus rhythm. Ninety per cent or more of all cases are reverted to sinus rhythm[1] and the incidence of complications is less than 3 per cent.[2] However, Lown and associates[3] showed in dogs undergoing repeated alternating current (A.C.) shocks that 90 per cent developed electrocardiographic changes of myocardial infarction and that 35 per cent died within one week. So there is a possibility that myocardial damage may follow D.C. shock. In an attempt to assess this, we followed serum enzyme levels in patients after D.C. countershock and we compared them with enzyme levels seen following appendectomy.

Patients and methods

Creatine phosphokinase (C.P.K.) was determined with C.P.K. Calsuls (Calbiochem). The method is based on Rosalki's[4] modification of the method of Oliver. Serum glutamic oxaloacetic transaminase (S.G.O.T.) was determined by the method of Babson and associates[5] modified for use on an autoanalyzer. Enzyme levels were considered to be of pathological significance above 70 units for C.P.K. and 35 units for S.G.O.T.

Serial estimations of C.P.K. and S.G.O.T. were performed on eight patients undergoing D.C. countershock. Details of these patients are given in Table I. All patients had atrial fibrillation except No. 7 who had atrial flutter. Oral procaineamide, 250 to 500 mg., was administered at six hour intervals commencing one or two days before reversion and continuing afterwards. Sleep was induced with an intravenous injection of diazepam (Valium), 10 to 20 mg., given one hour after 200 mg. of oral pentobarbitone sodium. In three cases 100 to 200 mg. of thiopentone sodium was required before the D.C. shock was applied to the chest. Electrodes were placed over the upper sternum and either over the cardiac apex or under the left scapula. The total electrical energy required for reversion varied from 20 to 750 watt seconds. Enzyme studies were performed before reversion and daily for three days after reversion. Of the eight patients, all except No. 3 reverted to sinus rhythm and there were no complications.

A second series of enzyme studies was performed on six patients undergoing appendectomy. Samples were collected before

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Table I Details of patients undergoing coun ershock

Patient No	Sex	Age	Diagno is nd history	No of shocks	Total electrical energy (watt-sec)	Max SGOT (units)	Max CPK (units)
1	M	39	Thyrotoxicosis and atrial fibrillation. Subtotal thyroidectomy 2 weeks ago	1	20	32	218
	M	65	Atrial fibrillation followed severe attack of bronchitis 2 weeks ago	3	700	24	107
3	M	53	Two weeks atrial fibrillation following respiratory obstruction during general anesthetic for repair of hand lacerations	2	300	20	159
4	M	58	Chronic rheumatic valvular disease and trial fibrillation. Aortic and mitral Starr-Edwards prosthesis 7 months ago	4	50	22	95
5	M	50	Mi tral valv disease and chronic atrial fibrillation. Starr Edwards prosthesis 3 months ago	2	150	30	77
6	F	56	Chronic rheumatic heart disease and atrial fibrillation. Mitral Starr-Edwards prosthesis 2 months ago	2	300	12	52
7	M	56	Alcoholic with cardiomyopathy and trial flutter with ariable block for over two weeks	3	270	28	26
8	M	54	Six months congestive cardiac failure and atrial fibrillation probably of ischemic origin	1	200	22	21

Patient to revert to sinus rhythm.

Tabl II Detail of patients undergoing appendectomy

Patient No	Sex	Age	Diagnosis	M x S.G.O.T	Max C.P.K
9	M	39	Acute appendicitis	44	261
10	F	21	Acute appendicitis	36	184
11	M	20	Acute appendicitis	28	133
12	M	20	Acute appendicitis	52	199
13	F	19	Acute appendicitis	24	57
14	F	67	Subacute appendicitis	16	40

operation six hours after operation and then daily for two days (Table II) In each case the patient was well prior to the attack of appendicitis. Appendectomy was carried out through a McBurney incision and the postoperative course in each case was uneventful An electrocardiogram (ECG) was done on each patient in the postoperative period and showed no abnormality

Results

Results of the enzyme studies after D C countershock are shown in Fig 1 and those after appendectomy in Fig 2

Following eversion C P K levels rose significantly in six of the eight patients being above the normal range n five The high initial value in No. 1 was considered to be due to subtotal thyroidectomy having been performed 14 day previously In no case did S G O T levels rise above normal limits. Four of the patients undergoing appendectomy showed a rise in C P K and in three the S G O T was also elevated

Discussion

Oram and associates performed S G O T and serum glutamic pyruvic transaminase (S G P T) estimations before and 24 hours

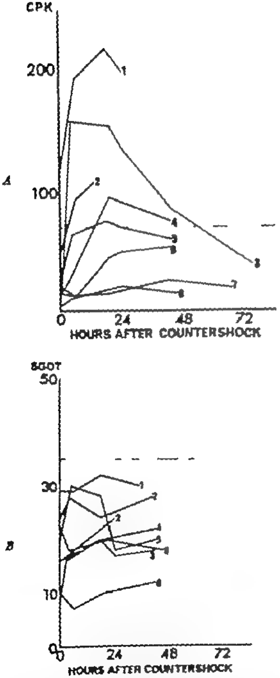

Fig. 1. Enzyme values following countershock treatment. Case numbers as in Table I. Dashed line indicates upper limit of normal. (*A*) C.P.K. values (upper limit of normal 70 I.U. per liter at 30° C.). (*B*) S.G.O.T. values (upper limit of normal 35 I.U. per liter at 37° C.)

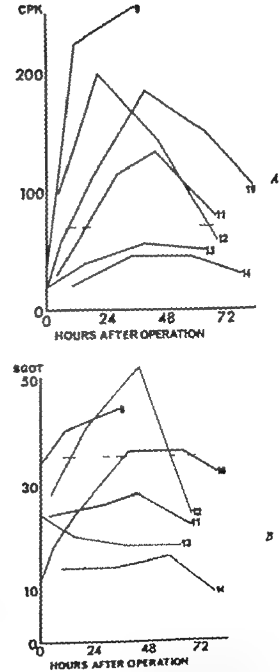

Fig. 2. Enzyme values following appendectomy. Case numbers as in Table II. Normal values as in Fig. 1. (*A*) C.P.K. values. (*B*) S.G.O.T. values.

after D.C. countershock in ten patients and concluded that there was no evidence that any serious damage resulted. Castle and Hecht[4] reported 15 cases of arrhythmias in 13 patients who were reverted to sinus rhythm without any subsequent rise in S.G.O.T. In the case described by Kong and co-workers,[8] 140 shocks were given over four days and yet at autopsy on the fourth day there was no macroscopic or microscopic evidence of myocardial necrosis. There is some evidence, however, that tissue damage follows D.C. reversion. Castle and Hecht[4] gave six shocks to the intact chests of each of 14 dogs. S.G.O.T. levels rose in 13 of the 14 dogs but the dogs remained well and at autopsy one month later histological section of their hearts showed no abnormality. The rise in S.G.O.T. levels was considered to be due to marked muscle contraction as similar enzyme changes followed D.C. shocks applied across the thigh muscles of other dogs. Slodki and associates[9] performed serial enzyme estimations on 27 patients who underwent 31 shocks for reversion of various arrhythmias and found raised S.G.O.T. levels in eight cases, the highest value reached being 150 units. These results suggested some tissue damage and it was concluded that the source of the enzyme was either cardiac or skeletal muscle. Serial ECG's, however, showed no evidence of myocardial ischemia. Slodki and associates also quote unpublished observations of increased C.P.K. levels after countershock in three out of six patients. In 75 per cent of our cases, C.P.K. rose markedly above the initial value while the levels of S.G.O.T. remained normal. C.P.K. is a particularly sensitive index of striated muscle damage and even rises after severe physical exertion.[11] Studies were performed on the patients undergoing appendectomy to compare the type and extent of enzyme changes produced by skeletal muscle damage with those seen after countershock or myocardial infarction. Appendectomy through a McBurney incision involves splitting rather than incision of muscle and it can be seen that even with this mild muscle trauma moderate elevations of C.P.K. and S.G.O.T. may occur. C.P.K. is generally considered to be a more sensitive index of skeletal muscle damage than S.G.O.T. Ayres and Willard[12] finding a rise in S.G.O.T. in only 24 of 217 surgical cases (excluding operations on the biliary tract).

In the patients who received countershock, there was no rise in S.G.O.T. in spite of abnormal levels of C.P.K. in five of them. The levels of C.P.K. seen in some of these patients after reversion are well within the range of values seen in myocardial infarction,[13] but if this was due to myocardial damage, then one would expect a concurrent significant rise in S.G.O.T. to be present. It is possible, however, that the mechanism of myocardial injury in electrical shock is different from that in ischemia. However, in view of the powerful intercostal muscle contractions that often attend the application of countershock and the uneventful postreversion course, it is more probable that C.P.K. is released from skeletal rather than cardiac muscle. If C.P.K. is released from skeletal muscle, we would expect higher levels in those patients with well developed muscles, inadequate anesthesia and more numerous shocks. In our series, it can be seen that the total number of shocks applied has no obvious relationship to the resulting level of C.P.K. Our series, however, is too small to assess these factors. At the moment, no isoenzyme technique is available for the differentiation of skeletal from myocardial C.P.K. and the determination of the actual source of the C.P.K. must await this development.

The diagnosis of myocardial infarction occasionally depends on enzyme studies. The results of C.P.K. estimations in those patients who have had recent countershock or electrical defibrillation must be interpreted cautiously in view of the fact that such a procedure alone may cause abnormal values in 50 per cent of cases.

Summary

Serial C.P.K. and S.G.O.T. estimations were performed on eight patients undergoing D.C. countershock. C.P.K. levels rose to abnormal levels in five, while the S.G.O.T. values showed no rise. Serial enzyme studies in six patients following appendectomy showed rises in C.P.K. in four and in S.G.O.T. in three patients. The possible sources of the C.P.K. following reversion were discussed and it was

concluded that enzyme release followed powerful intercostal muscle contractions.

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REFERENCES

1. Robinson, J S., Sloman, G. Hjorth, R. J and Goble, A. J Direct current countershock in cardiac arrhythmias, M J Australia 1:289 1965
2. Morris, J J Peter R. H., and McIntosh, H D Electrical conversion of trial fibrillation. Immediate and long-term results and selection of patients, Ann. Int. Med. 65:216, 1966.
3. Lown, B., Amarasingham, R., and Neuman, J New method for terminating cardiac arrhythmias. Use of synchronized capacitor discharge, J.A.M A. 182:548, 1962.
4. Rosalki, S. B. A capsule test for creatine phosphokinase, Proc. A. Clin. Biochem. 4 23 1966
5. Oliver 1 T Spectrophotometric method for the determination of creatine phosphokinase and myokinase, Biochem. J 61 116, 1955
6. Babson, A. L., Shapiro, P O Williams, P A R., and Phillips, G. E. The use of a diazonium salt for the determination of glutamic-oxaloacetic transaminase in serum, Clin. chim. acta 7 199 1962.
7. Oram, S., Davies J P H Weinbren, I Taggert, P nd Kitchen, L. D Conversion of atrial fibrillation to sinus rhythm by direct current shock, Lancet 2 159 1963
8. Castle, C. H., and Hecht, H H Evaluation of adverse effects on the heart of direct current shocks to the intact chest, Clin. Res. 12 77 1964.
9. Kong, T Q and Proudfit, W L Repeated direct current countershock without myocardial i jury J.A.M.A. 187:60, 1964
10. Slodki, S. J Falicov R. E., Katz, M J West, M and Zimmerman, H. J Serum enzyme changes following external direct current shock therapy for cardiac arrhythmias, Am. J Cardiol. 17 792 1966
11. Griffiths, P D Serum creatine kinase and exercise, Brit. M J 2 167 1965.
12. Ayres, P R. and Willard, T B Serum glutamic oxaloacetic transaminase in 266 surgical cases, Ann. Int. Med 52:1279 1960.
13. Griffiths, P D ATP Creatine phosphotransferase in the diagnosis of acut chest pain, Brit. Heart J 28 199 1966.

Urinary excretion of free norepinephrine and free epinephrine in patients with acute myocardial infarction in relation to its clinical course

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Increased activity of the sympathoadrenal system has been shown in patients with acute myocardial infarction evidenced by augmented urinary excretion of free epinephrine and norepinephrine and their metabolite—3-methoxy-4-hydroxymandelic acid—during the acute phase of myocardial infarction.[1-4] Increased blood catecholamine concentration has also been observed.[5] Recently it has been emphasized in patients with myocardial infarction that the urinary excretion of free norepinephrine and epinephrine is related to the severity of the clinical course. This problem deserves special attention in connection with the marked influence of catecholamines on cardiac function.

The purpose of our study was to investigate the relationship between the urinary excretion of catecholamines and the nature of complications in a larger group of patients with myocardial infarction.

Material and methods

Observations were made on 19 patients (13 men and 6 women) 40 to 66 years of age. In each case, the diagnosis of recent myocardial infarction was confirmed by typical electrocardiographic changes and enzymatic alterations in the blood. The collection of urine was started not later than 12 hours from the onset of the disease. All of the patients were admitted to the Coronary Care Unit where they remained for seven days under continuous electrocardiogram (ECG) monitoring with frequent pulse and blood pressure measurements. Daily estimations of urinary catecholamine excretion were obtained throughout this period. Later the patients were transferred to the ward where further examinations of catecholamines in the urine were performed until their excretion returned to normal.

In three patients, the clinical course was uncomplicated. One patient was in shock on the first day of hospitalization and received intravenous norepinephrine for two days. Another patient required a brief treatment with intravenous norepinephrine for a marked hypotension. In one patient the myocardial infarction was complicated by pulmonary edema, which occurred on the first day in the hospital. Disturbances in the cardiac rhythm complicated the clinical course

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in six patients. In five of the patients, multiple ventricular ectopic beats persisted for from one to four days. In one patient, an episode of paroxysmal atrial fibrillation appeared on the fourth day. Four patients had tachycardia with heart rates ranging between 110 and 140 per minute and lasting for 2 to 4 days. In four patients, hypotonia occurred (systolic arterial pressure 85 mm. Hg and below). Urinary excretion of free norepinephrine (recovery 88 per cent ± 12) and epinephrine (recovery 86 per cent ± 9) was determined by the spectrofluorometric methods described by Euler and Lishajko.[8] A sample of 25 ml. from a 24 hour urine collection was taken. The extraction of catecholamines from the urine was performed by adsorption on aluminum oxide at pH 8.2 to 8.3 followed by elution with 0.25N acetic acid. The fluorescence was brought about by oxidation with ferricyanide and stabilized by alkaline ascorbic acid solution. The fluorescence was measured by the fluorimeter constructed according to the principle given by Weil-Malherbe and Bone[7] connected with the registration system of Beckman's spectrophotometer. The measurement was made at two different fluorescence wave lengths. The fluorescence was determined with two filter sets. Filter set A consisted of a primary interference filter 395 mμ for excitation combined with a secondary filter (peak transmission 490 mμ). Filter set B was composed of a 436 mμ interference filter for excitation with a secondary filter with peak transmission at 540 mμ.

The mean excretion of free norepinephrine and epinephrine in normal subjects was for norepinephrine 25.2 ± 6.6 μg per 24 hours and for epinephrine 4.3 ± 1.6 μg per 24 hours. The arithmetic mean of excretion ± twice the S.D. was accepted as a limit of normal value. All patients were maintained on a normal diet throughout the study. They were not receiving quinidine, tetracycline, or other drugs which are known to interfere with the estimation of catecholamines. The determinations of free norepinephrine and epinephrine obtained from the days during which two patients were receiving norepinephrine intravenously were not included.

Results

The mean excretion of free norepinephrine in the whole group was elevated during the first five days. The highest values were observed during the first two days. Later, a gradual decline in excretion was found. The mean excretion of free epinephrine during the first days of the disease was higher than that during the next days, but it did not exceed the upper limit of the normal level.

The results of the mean excretion of free norepinephrine and epinephrine are illustrated in Fig. 1.

The highest norepinephrine excretion, reaching 90 μg for 24 hours or more, was seen in four patients (Cases 1, 2, 3, and 4—Fig. 2).

In Patient S. B., the symptoms of shock and heart decompensation were present during the first two hospital days. On the second day, ventricular tachycardia occurred with a brief episode of ventricular fibrillation. Since the patient received intravenous infusions of norepinephrine, the determinations of norepinephrine excretion in the first three days were not performed. On the fourth day a high increase in urinary excretion of norepinephrine (103 μg per 24 hours) was seen; the excretion of epinephrine was at the upper

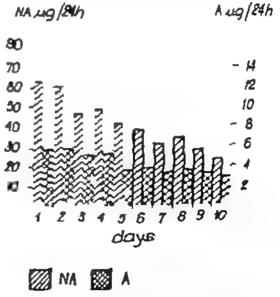

Fig. 1. The mean urinary excretion of free norepinephrine and free epinephrine in 19 patients with recent myocardial infarction.

limit of the normal level (6 9 μg per 24 hours) During the following days, the urinary excretion of norepinephrine showed a tendency to decline, but still remained elevated. On the seventh hospital day the urinary excretion of epinephrine rose to 9 μg per 24 hours and on the following day the patient developed irreversible shock and died

Patient B M had two episodes of pulmonary edema on the day of admission and ventricular ectopic beats were also observed During the subsequent two days, signs of cardiac decompensation were evident. On the fourth day transient hypotonia occurred and lasted a few hours. During the 7 days after admission, persistent tachycardia was present. Increased excretion of norepinephrine was noted until the eighth hospital day Furthermore,

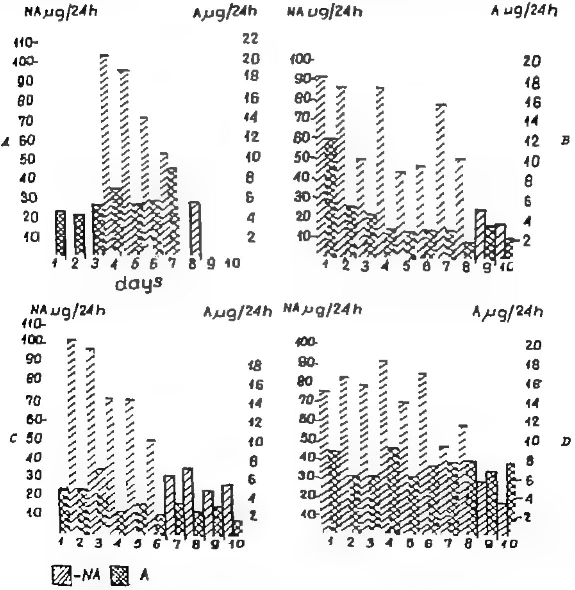

Fig 2. Four patients with recent myocardial infarction exhibiting the highest urinary excretion of free norepinephrine (*A* Case 1 S. B.; *B* Case 2, B. M.; *C*, Case 3 S. K. *D* Case 4 J M). I each case, the clinical course was complicated (for details see text).

on the first day a distinct increase in urinary excretion of free epinephrine (12 µg per 24 hours) was found

In Patient S K elevated excretion of norepinephrine was observed on the second third fourth fifth and sixth days after admission On the first hospital day the patient received a brief infusion of norepinephrine and the excretion of this amine was not estimated On the first day a brief episode of hypotonia was observed a striking tachycardia (more than exceeding 130 beats per minute) persisted during the following days Urinary excretion of free epinephrine was normal

In Patient J M the urinary excretion of norepinephrine remained elevated for 8 days. The highest value (90 2 µg per 24 hours) was found on the fourth day Urinary excretion of free epinephrine was

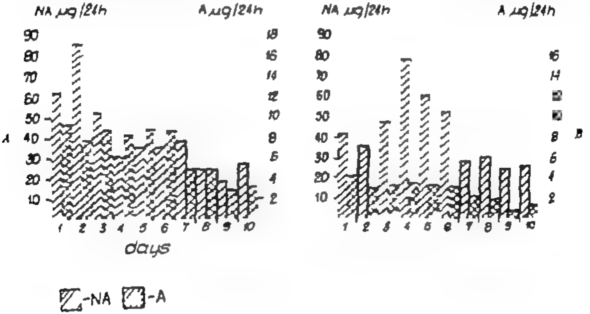

Fig 3 Two patients with recent myocardial infarction in whom the time relationship between the increase in urinary excretion of free norepinephrine and a fall of blood pressure was seen (A Case 5 J K. B Case 6 Z. R.).

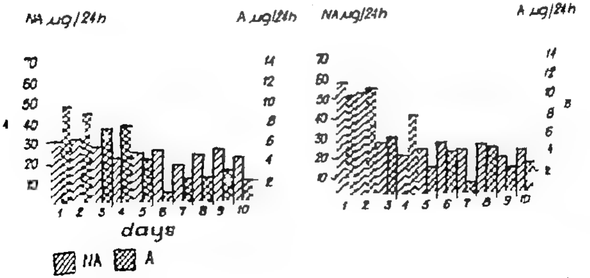

Fig 4 Two cases of recent myocardial infarction with the highest urinary excretion of free epinephrine at the time when the disturbances of cardiac rhythm were observed (A Case F W J B Case 8 Z. M).

also increased (the highest value was seen on the fourth day—8 9 μg per 24 hours) Persistent tachycardia, which lasts for several days, was a characteristic clinical feature.

Particular consideration should also be given to patients who did not exhibit values of catecholamines so high as those of the patients mentioned above but in whom a time relationship between the increased epinephrine and/or norepinephrine excretion and the onset of clinical complications was evident.

In two patients (Cases 5 and 6) the highest value of urinary excretion of norepinephrine was observed on the day when a fall of systolic arterial pressure below 80 mm Hg occurred (Fig 3) In Patient J K this took place on the second day (urinary excretion of norepinephrine 85.3 μg per 24 hours) and in Patient Z. B on the fourth day after the onset of the disease (79 8 μg per 24 hours)

Patient W J (Case 7) displayed normal excretion of norepinephrine, but an increased excretion of epinephrine was observed during the first four hospital days (Fig 4) at that time the patient had multiple ventricular extrasystoles. In the further clinical course, disturbances of cardiac rhythm did not recur and urinary excretion of free epinephrine was normal

Similar observations were made in Case 8 (Z. M) in whom disturbances of cardiac rhythm and elevated excretion of epinephrine lasted for four days after admission.

In Case 9 (T N) the excretion of norepinephrine was increased during three days following the onset of myocardial infarction, but the excretion of epinephrine was increased only on the first day (9 7 μg per 24 hours) (Fig 5) On the same day the patient had tachycardia (140 beats per minute) and ventricular extrasystoles. These disturbances disappeared later

In Patient L. J (Case 10) an episode of paroxysmal atrial fibrillation occurred on the fourth hospital day coinciding with the highest epinephrine excretion of 7.0 μg per 24 hours.

In the patient A. S. (Case 11) the urinary excretion of epinephrine rose to 8.8 μg per 24 hours on the fourth day of observation and remained elevated during the following three days. Multiple ven-

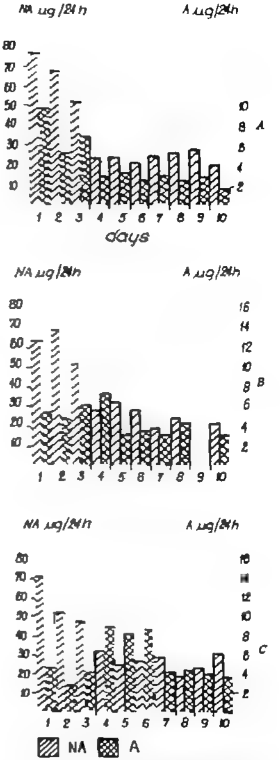

Fig 5 Three patients with recent myocardial infarction in whom time relationship between the increase of urinary excretion of free epinephrine and the onset of disturbances of cardiac rhythm were seen (A, Case 9 T.N B Case 10 L J C, Case 11 A. S.).

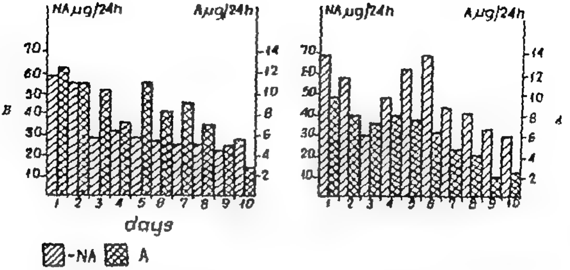

Fig 6 The increased urinary excretion of free epinephrine in two patients with recent myocardial infarction complicated by persistent tachycardia and ventricular extrasystoles (*A* Case 12, A. J. *B* Case 13 S. Z.). *Case 13 also illustrates the increase of free norepinephrine excretion occurring again during the period of transient hypotonia.*

tricular ectopic beats were recorded during that period The urinary excretion of free norepinephrine at that time was normal A moderate increase in the urinary excretion of norepinephrine was noted in this patient only during the first three days.

An increased excretion of epinephrine was observed also in Cases 12 and 13 (Fig 6) In the patient A. J the increase lasted for 8 days an elevated excretion of norepinephrine was observed only on the first day Persisting heart failure and recurring ventricular extrasystoles were present in this patient Patient S. Z excreted increased amounts of norepinephrine during the initial six hospital days and of epinephrine during the initial five days It should be pointed out that her clinical course was complicated by persisting tachycardia recurring extrasystoles and on the fifth hospital day a transient fall in blood pressure.

Five patients (Cases 14 15 16 17 and 18) showed moderate increase of norepinephrine excretion in all but one it returned to normal on the third or fourth day (Fig 7) The excretion of free epinephrine was normal. With the exception of one patient with mild tachycardia the clinical course was uneventful. In Case 19 (W S.) urinary excretion of catecholamines was normal throughout the whole period of observation and no clinical complications occurred (Fig 8)

Discussion

Our study confirms the reports of other workers[4,5] demonstrating an increased urinary excretion of catecholamines during the acute phase of myocardial infarction. A detailed clinical analysis of the patients under study reveals individual differences in the magnitude of this increase and in the interrelationship between the urinary excretion of free epinephrine and that of free norepinephrine An increased excretion of norepinephrine was a more constant feature the observed values of free norepinephrine in the urine exceeded the highest level of the normal values in 17 and those of epinephrine—in 11 of 19 patients with acute myocardial infarction. The most pronounced and most persistent increase in the urinary excretion of catecholamines was usually found in patients with severe myocardial infarction complicated by shock acute left ventricular failure and cardiac arrhythmias.

Special consideration should be given to the patients who displayed a time relationship between the excretion of epinephrine and/or norepinephrine and the onset of clinical complications. This relationship was particularly evident with

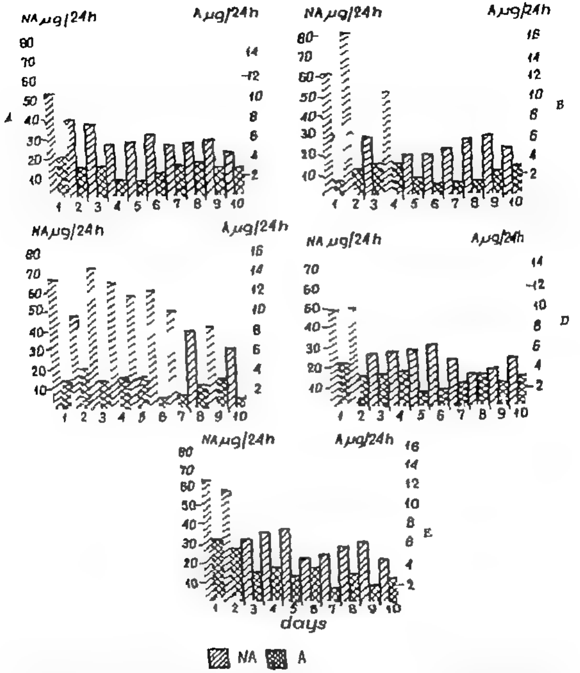

Fig. 7. Moderate increase of urinary excretion of free norepinephrine in five cases of myocardial infarction with uneventful clinical course. In all but one, it returned to normal during a few days (*A*, Case 14, J. [redacted]; *B*, Case 15, T. J.; *C*, Case 16, J. G.; *D*, Case 17, J. K.; *E*, Case 18, A. W.).

epinephrine. Out of 11 patients who excreted increased amounts of epinephrine disturbances of cardiac rhythm were noted in 9; in the majority of them a time relationship could be demonstrated between the increase of the urinary free epinephrine and the onset of complications. On the contrary, in the group of 8 patients who excreted normal amounts of epinephrine throughout the study, there was only one episode of transient cardiac arrhythmia. Free norepinephrine excretion was particu-

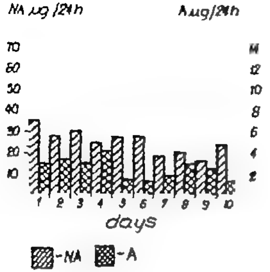

Fig. 8. Normal excretion of catecholamines in a case of uncomplicated myocardial infarction (Case 19 W. S.).

larly high in cases complicated by shock and/or heart failure. In two patients a transient fall in blood pressure was concomitant with an increase in the excretion of free norepinephrine. The lowest values of urinary catecholamine excretion were found in uncomplicated cases of myocardial infarction. Our observations are in agreement with a recent report of Valori and associates,[5] who demonstrated an increased excretion of norepinephrine in a case of myocardial infarction complicated by a fall in blood pressure and a marked elevation of epinephrine excretion in cases of myocardial infarction with arrhythmia. These authors found an increased excretion of both catecholamines in severe myocardial infarction in contrast to the uncomplicated course of myocardial infarction when only a transient and insignificant increase of epinephrine occurred. Our study may demonstrate an enhanced activity of the sympathoadrenal system in acute myocardial infarction. The results obtained may also represent an alteration in the pattern of excretion of the catecholamines or disturbance in catecholamine storage capacity of the kidney or other tissues. Our results suggest that the excretion of catecholamines may vary in relation to the severity of the clinical course and to the nature of concomitant complications. However, our data do not provide evidence for the causal relationship between these phenomena. In view of the significance of the sympathoadrenal system in the regulation of cardiovascular function, further investigations seem desirable in order to elucidate the role of the sympathoadrenal activity in the clinical course of myocardial infarction.

Summary

Serial estimations of urinary excretion of free norepinephrine and epinephrine were made in 19 patients with recent myocardial infarction of varying clinical courses. An increase in urinary excretion of catecholamines during the acute phase was noted, more distinct in cases characterized by severe clinical course. In patients with myocardial infarction complicated by shock, circulatory insufficiency, and transient fall in blood pressure the urinary excretion of free norepinephrine was more significantly elevated than that of epinephrine. The urinary excretion of free epinephrine was more enhanced in patients with myocardial infarction complicated by disturbances in cardiac rhythm. The results suggest a relationship between the clinical course of myocardial infarction and the activity of the sympathoadrenal system.

REFERENCES

1. Nuzum, E. R., and Bischoff, F.: The urinary output of catechol derivates including adrenaline in normal individuals, in essential hypertension, and in myocardial infarction, Circulation 7:96, 1953.
2. Raab, W., and Gigee, W.: Urinary 3-methoxy-4-hydroxymandelic acid (VMA) in ischemic heart disease and ischemia, Am. J. M. Sc. 220:547, 1965.
3. Aleksandrow, D., Januszewicz, W., and Wocial, B.: Wydalanie noradrenaliny, adrenaliny oraz kwasu wanilinomigdałowego w moczu w zawale serca, Pol. Arch. Med. Wewn. 36:437, 1966.
4. Gazes, P. C., Richardson, J. A., and Woods, E. F.: Plasma catecholamine concentration in myocardial infarction and angina pectoris, Circulation 19:657, 1959.
5. Valori, C., Thomas, M., and Shillingford, J. P.: Urinary excretion of free noradrenaline and adrenaline following acute myocardial infarction, Lancet 1:127, 1967.
6. Euler, U. S., and Lishajko, F.: Improved technique for the fluorometric estimation of catecholamines, Acta physiol. scandinav. 51:348, 1961.
7. Weil-Malherbe, H., and Bone, A. D.: The adrenergic amines of human blood, Lancet 1:974, 1953.

Experimental and laboratory reports

Differences in the relationships between coronary blood flow and myocardial clearance of isotopes of potassium, rubidium and cesium

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Isotopes of potassium (K), rubidium (Rb), and cesium (Cs) have been used for studies of myocardial blood flow that use external counting.[1-3] Although the relationship between the rate of myocardial uptake of Rb^{86} from arterial blood and the simultaneous rate of coronary blood flow has been extensively studied,[4-7] there are few similar data regarding isotopes of K and Cs. K^{42} and Cs^{131} are of clinical interest because the subject receives less radiation when they are used than when Rb^{86} is employed. Therefore, the rates of coronary blood flow and myocardial clearance of K^{42}, Rb^{86}, and Cs^{131} were determined simultaneously in dogs.

Materials and methods

In six dogs ranging in weight from 17.2 to 20.8 kilograms, anesthetized with 27 mg. per kilogram of pentobarbital, arterial and coronary sinus blood were aspirated continuously at a constant rate during a 10 minute intravenous infusion of a mixture of K^{42}, Rb^{86}, and Cs^{131}. The tracers were injected at a gradually decreasing rate, thus, maintaining a plateau concentration of isotope in arterial blood. An adequate range of coronary blood flow rates was obtained by performing phlebotomy or transfusion prior to measurements. When phlebotomy was used, the blood pressure stabilized at the low level for a sufficient period of time to complete the experiment. In the studies where transfusion was used, the selected blood pressure was maintained by a variable speed Sigmamotor pump. Upon completion of the tracer infusion, the hearts were removed and the concentration of each tracer in blood and myocardium was determined. The 1.51 mev. γ ray emission of K^{42} was first counted with a NaI scintillation detector. By adjusting the window of the pulse height analyzer to count only the K^{42} peak, the γ rays of Cs^{131} and Rb^{86} were excluded. After a delay of one week, during which the K^{42} decayed to negligible amounts, counting was repeated with the pulse height analyzer window set to count the γ peak of Rb^{86} and later the peak of Cs^{131}. The amount of each tracer in each sample was then

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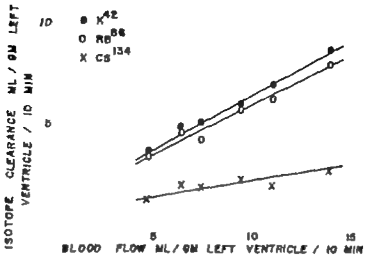

Fig. 1. The relationship between the rate of coronary blood flow and the simultaneous rates of myocardial clearance of K^{42}, Rb^{86}, and Cs^{134} in dogs.

calculated by standard techniques. The mean rates of coronary blood flow were calculated by applying the Fick principle to the myocardial isotope uptake. Isotope clearance was determined from the mean concentrations of isotope in the blood and in the myocardium.

Results

The results are shown in Fig. 1. Coronary blood flow ranged from 4.6 to 13.8 ml. per gram, averaging 8.7 ml. per gram of left ventricle per 10 minutes. The results with Rb^{86} were consistent with those of previous studies.[7] An average of 65 per cent (range 58 to 76 per cent) of the Rb^{86} was cleared from arterial blood during one passage through the myocardium. The clearance of K^{42} was slightly greater than that of Rb^{86} in each instance, averaging 71 per cent (range 64 to 80 per cent). In contrast, only 22 per cent of the Cs^{134} in arterial blood was removed during one passage through the heart (range 9 to 30 per cent). For a given increase in flow, clearance of K^{42} and Rb^{86} increased an average of 3.2 times more than did that of Cs^{134}. A relationship between flow and clearance of isotope was apparent in each case. When these were calculated as linear regression equations, the mean errors in estimating coronary flow from its mean relationship to isotope clearance were: K^{42} 4 per cent, Rb^{86} 7 per cent, and Cs^{134} 15 per cent.

Discussion

The rate at which these isotopes are taken up by the myocardium is determined by the rate of coronary blood flow and by the rate of exchange of the element between the circulating blood and the myocardial cell. The exchange of K^{42} and Rb^{86} across the cellular wall of human erythrocytes is nearly the same, while Cs^{134} enters much more slowly.[8] The present studies indicate that there are differences in the rates of cellular flux of K, Rb, and Cs in the myocardial cell which are similar to those in erythrocytes. The greater the rate of transcellular myocardial exchange in relation to the rate of coronary blood flow, the more nearly isotope uptake becomes a flow limited process. These differences in cellular flux result in a favorable relationship between flow and clearance for tracers of K and Rb, but a poor one for Cs isotopes. Therefore, measurements of regional rates of myocardial uptake of isotopes of Cs appear to be a less promising means for visualizing differences in regional myocardial rates of blood flow than do determinations of K or Rb uptake rates.

Summary

Since isotopes of K, Rb, and Cs reach high concentration in the myocardium following their intravenous injection, any of the aforementioned isotopes can be used to determine regional myocardial

clearance by employing external counting techniques. It has been established by previous studies that the rate at which Rb^{86} is cleared from the arterial blood is closely related to the rate of coronary blood flow. K^{42} and Cs^{134} offer the advantage of reduced radiation load when used in man. Therefore, the relationship between the rate of coronary blood flow and the rate of myocardial clearance of K^{42} and Cs^{134} was determined in dogs, and compared to the simultaneous results obtained with Rb^{86}.

An average of 71 per cent of the K^{42} in arterial blood was removed by the myocardium during one circulation while 65 per cent of the Rb^{86} was extracted. Only 22 per cent of the Cs^{134} entered the myocardium under the same conditions. As a result, Cs^{134} clearance was substantially less reliable than K^{42} or Rb^{86} clearance as an index of the rate of coronary blood flow.

REFERENCES

1. Love, W. D., and Burch, G. E.: Estimation of the rates of uptake of Rb^{86} by the heart, liver and skeletal muscle of man with and without cardiac disease, Internat. J. Appl. Rad. & Isotopes 3:207, 1958.
2. Carr, E. A., Jr., Beierwaltes, W. H., Patno, M. E., Bartlett, J. D., and Wegst, A. V.: The detection of experimental myocardial infarcts by photoscanning, Am. Heart J. 64:650, 1962.
3. Carr, E. A., Jr., Walker, B. J., and Bartlett, J., Jr.: The diagnosis of myocardial infarcts by photoscanning after administration of cesium[131], J. Clin. Invest. 42:922, 1963.
4. Cohen, A., Gallagher, J. P., Luebs, E., Varga, Z., Yamanaka, J., Zaleski, E., Bluemchen, G., and Bing, R. J.: The quantitative determination of coronary flow with a positron emitter (rubidium[84]), Circulation 32:636, 1965.
5. Donato, L., Bartolomei, G., and Giordani, R.: Evaluation of myocardial blood perfusion in man with radioactive potassium or rubidium and precordial counting, Circulation 29:195, 1964.
6. Love, W. D.: Isotope clearance and myocardial blood flow, Am. Heart J. 6 :579, 1964.
7. Love, W. D., Tyler, M. D., Abraham, R. E., and Munford, R. S.: Effects of O_2, CO_2, and drugs on estimating coronary blood flow from Rb^{86} clearance, Am. J. Physiol. 208:1206, 1965.
8. Love, W. D., and Burch, G. E.: A study in dogs of methods suitable for estimating the rate of myocardial uptake of Rb^{86} in man, and the effect of l-norepinephrine and Pitressin on Rb^{86} uptake, J. Clin. Invest. 36:468, 1957.
9. Love, W. D., and Burch, G. E.: A comparison of potassium[42], rubidium[86], and cesium[134] as tracers of potassium in the study of the cation metabolism of human erythrocytes in vitro, J. Lab. & Clin. Med. 41:351, 1953.

Pulmonary and systemic hemodynamic effects of cardiac glycosides

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Many physiological actions of digitalis glycosides have been elucidated only recently, although their effects in reversing congestive heart failure and slowing the heart rate have long been known.[1-4] These drugs increase myocardial contractility and produce generalized vasoconstriction with consequent increase in systemic resistance. In some species they also evoke constriction of the hepatic veins, with resultant splanchnic pooling. These actions are similar in normal subjects and those with congestive cardiac failure, but cardiac output varies with the way in which venous return is altered. In contrast to the extensive information on cardiac and systemic actions, little is known of the way in which digitalis glycosides affect the lung circulation.[1-4] Because of the potential importance of digitalis-induced vasoconstriction on the pulmonary vasculature, this report concerns the effects of acetyl strophanthidin, strophanthidin (ouabain), and digoxin on the pulmonary as well as systemic circulation of the intact unanesthetized dog.

In additional experiments, to eliminate the possible role of altered right or left heart dynamics, a preparation was devised in which a mechanical pump replaced the right heart and maintained pulmonary blood flow constant. Concurrently, left atrial pressure was maintained at control level after glycoside injection.

Methods

Under sterile conditions, left thoracotomy was performed in ten anesthetized dogs weighing between 20 to 25 kg. Polyvinyl catheters were secured in the left atrium, main pulmonary artery, and aorta and were filled with heparin solution to prevent clotting.[7] An electromagnetic flow probe was placed around the ascending aorta, and catheters and flow probe wires were brought through the chest wall and tunneled subcutaneously to exit at the back of the dog's neck. Postoperatively the animals received appropriate analgesics and antibiotics for one week. At the end of that time, after pressures and aortic flow were stable for a three day period

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experiments were performed. Awake unsedated postoperative dogs were trained to lie quietly in the prone position in a specially constructed box while pressure, flow, and electrocardiographic measurements stabilized. Heart rate (HR), peak stroke velocity (S Vel), cardiac output (CO), systolic, diastolic, and *mean* aortic pressures (SAP), pulmonary arterial systolic, diastolic, and *mean*-pressure (PAP), left atrial pressure (LAP), instantaneous pulmonary vascular pressure gradient (PVPG = pulmonary artery minus left atrial pressure), and electrocardiographic changes were monitored. With the animal in the prone position, it was assumed that LAP exceeded alveolar pressure and could therefore be used as the downstream pressure of the pulmonary bed. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated from the pressure and flow data by analogue computation. Stroke volume (SV) was derived from analogue computer integration of the forward flow portion of the S Vel curve. The acceleration of the first portion of this curve (dSV/dt) was determined by analogue differentiation of S Vel with a band pass of 0.4 – 290 cycles. Cardiac output measured in the ascending aorta was considered to be equivalent to pulmonary blood flow with no correction made for possible small changes in the proportion of coronary blood flow. Frequent measurements of arterial pH, pCO_2, and pO_2 were performed which confirmed the stability of oxygenation and acid base balance. Gated square wave electromagnetic flowmeter calibration was established *in vitro* and confirmed by simultaneous *in vivo* indocyanine green dye dilution outputs. Systemic pressure was measured with a P23GB Statham transducer and pulmonary artery and left atrial pressures were measured with a Sanborn 267B differential transducer which also permitted measurement of instantaneous pulmonary vascular pressure gradient. After a control period characterized by stability of parameters for at least ten minutes, acetyl strophanthidin 40 mcg. per kilogram (16 experiments), ouabain 40 mcg. per kilogram (22 experiments), or digoxin, 50 mcg. per kilogram (10 experiments) were injected directly into the pulmonary artery. By pretrial, these doses were selected as just under a therapeutic digitalizing level but sufficient to produce expected heart rate and systemic effects in most. Pressures and flows were recorded continuously over a subsequent 20 to 90 minute period. Experimental design included measurements for 40 minutes after acetyl strophanthidin and ouabain and for 90 minutes after digoxin injection, but some experiments were terminated earlier when the dog developed ventricular premature contractions, nausea, or vomiting. Dogs were used randomly for multiple experiments concerned with one or all digitalis agents, care being taken that sufficient time had elapsed for elimination of previous dosages. Control runs of similar duration were done without injection or following infusion of the same volume of normal saline to evaluate the effects of time and the experimental situation and to rule out placebo effect.

Data for each parameter for each minute after injection were compared with control levels. The mean control value was established for individual experiments by determining the mean value of each parameter for each of the 10 minutes preceding drug infusion. Percentage deviations following injection were determined by comparing each experimental minute value to its mean control. For left atrial pressure, absolute change rather than percentage deviation was plotted. The mean change from control for each parameter for each *minute* was tested for statistical significance. Average changes from control values were analyzed for statistical significance at intervals of 1, 2, 3, 4, 5, and 10 minutes. A two-sided T test ($p < 0.05$) was applied to each mean change to determine significance of difference from control.

To eliminate effects of altered right ventricular contractility, rate and output and to rule out changes in left heart function as a cause of the increase in pulmonary vascular resistance, the following preparation was devised (Fig. 1). In an anesthetized thoracotomized supine dog, all systemic venous blood from both cavas was drained into a reservoir from which it was pumped* at a fixed rate and volume into

*Harvard pulsatile pump, Model 1405

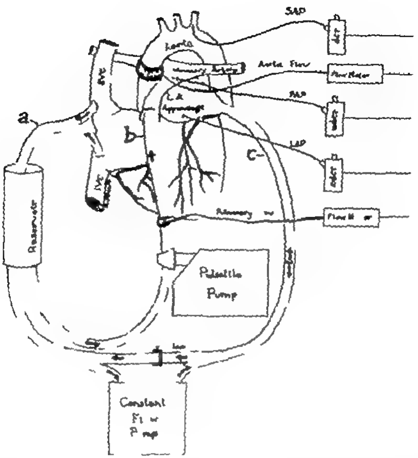

Fig. 1 Anesthetized thoracotomized dog with (a) venous drainage cannula from the inferior and superior vena cava, (b) line from pulsatile pump directed into the main pulmonary artery. Ligature at the base of the pulmonary artery limits the pulmonary blood flow to that of the pulsatile pump output, and (c) cannula into the left atrium through which blood can be drained by gravity into the reservoir or pumped with constant flow pump into the left atrium.

the pulmonary artery. Left atrial pressure was monitored on an oscilloscope at high gain and was maintained constant by infusing from or draining into the reservoir. It was possible to keep left atrial pressure within 1 mm. Hg of control during all measurements. Oxygen 100 per cent was administered by endotracheal tube to prevent hypoxia and arterial pH and pCO_2 were monitored and ventilation adjusted to maintain them in the normal range.

Results

Complete results for the unanesthetized dog experiments are shown graphically in Figs. 2, 3 and 4. A horizontal time axis shows minutes after drug injection while a separate vertical axis for each parameter shows the mean percentage change from control level (taken as 0). Data are presented as percentage change to allow a uniform method of depicting the mean change over time of all data and all dogs on a single graph. Absolute changes can be estimated by comparing these graphs to control values listed on the left. Mean values are shown as dots with the clear centered dots representing changes significant at a 5 per cent level.

All three cardiac glycosides produced expected and previously reported effects on cardiac and systemic hemodynamics. Acetyl strophanthidin and ouabain produced pulmonary vasoconstriction but these effects were not as obvious after digoxin administration for reasons to be discussed.

Acetyl strophanthidin. An initial rise of about 10 per cent in pulmonary artery pressure was followed by a significant

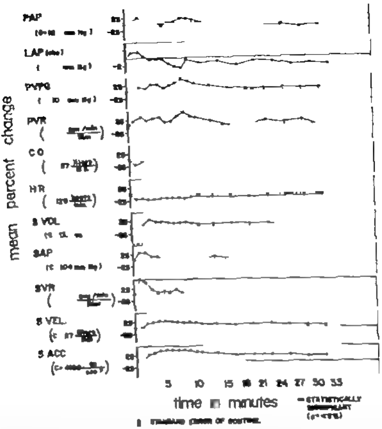

Fig. 2. Mean per cent changes in hemodynamic parameters (vertical axis) in minutes after injection of acetyl strophanthidin (horizontal axis). Summary of all experiments. The zero line for each parameter represents the mean control level for that measurement. Absolute mean control values are printed at the left of each individual graph. The standard error of control means is indicated by the dark, vertical bar at the left edge of each graph. All values are depicted as percentage change from control except for left atrial pressure, which is plotted in absolute change in millimeters of mercury.

Mean changes for the designated time period are indicated by black dot; those statistically significant at 5 per cent level are shown by clear dot. See text (under Methods) for meaning of abbreviation.

decrease in left atrial pressure for the duration of the study (Fig. 2). The percentage change in left atrial pressure was consistent and highly significant. Although this represented a fall in left atrial pressure of only 2 to 4 mm. Hg, it was sufficient to cause a consistently elevated pulmonary vascular pressure gradient. Since flow was unchanged except for an initial transient drop, pulmonary vascular resistance remained elevated (+20 to +35 per cent) for 30 minutes after acetyl strophanthidin injection, particularly during the first fifteen minutes.

Significant reduction in heart rate (−24 per cent) and elevation of systemic arterial pressure (+32 per cent) occurred within one minute after injection. An increase in systemic vascular resistance occurred only during the first 10 minutes after injection, following which both SAP and SVR returned to control levels. Cardiac changes including reduced heart rate, increased S Vel., and increased dSV/dt persisted throughout the entire observation period. Increased SV, related at least in part to reduced heart rate, also persisted.

In addition to previously reported positive inotropic and systemic vasoconstrictive effects, acetyl strophanthidin caused increased pulmonary vascular resistance. Since flow did not change and respiration remained constant, this increased PVR was thought to be caused by pulmonary vasoconstriction rather than mechanical vascular distending effects of increased flow

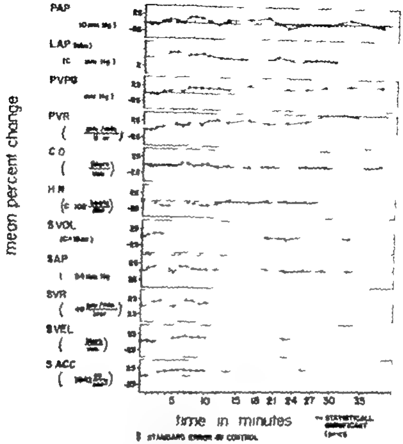

Fig. 3. Mean per cent changes in hemodynamic parameters (vertical axis) in minutes after injection of ouabain (horizontal axis). Summary of all experiments. The zero line for each parameter represents the mean control level for that measurement. Absolute mean control values are pri ted t the left of each individual graph. The standard error of control means is indicated by the dark, vertical bar at the left edge of each graph. All values are depicted as percentage change from control except for left atrial pressure, which is plotted in absolute change in millimeters of mercury.

Mean changes for the designated time period are indicated by a black dot; those tatistically significant at 5 per cent level are shown by a clear dot. See text (under Methods) for meaning of abbreviation.

or changes in respiration. Except for systemic vasoconstriction, all effects persisted throughout the duration of the experiment. Experiments were terminated at 40 minutes by design, but some were ended as early as 20 minutes because of ventricular premature contractions or excessive restlessness of the dog associated with nausea or vomiting.

Ouabain. PAP was slightly elevated (+10 per cent mean) for about 20 minutes after injection, while LAP was below control levels, particularly after the first ten minutes following ouabain administration (Fig. 3). Left atrial pressure fell later than following acetyl strophanthidin. The marked percentile change represents an absolute change of less than 2 mm. Hg from an initial control pressure of 0.1 mm. Hg. PVPG stayed consistently above control levels, but pulmonary vascular pressure changes were generally less marked and less significant than after acetyl strophanthidin. The effects of ouabain began slightly later and persisted longer. Flow remained at control levels, so PVR was increased for the entire period. PVR increase was more marked in the second 15 minute period than in the first, chronologically opposite to the effect of acetyl strophanthidin and related probably to the slower onset and longer duration of ouabain action.

Reduction in heart rate was less marked and persisted for only 15 minutes (−3 to −17 per cent). In contrast, increased SVel.

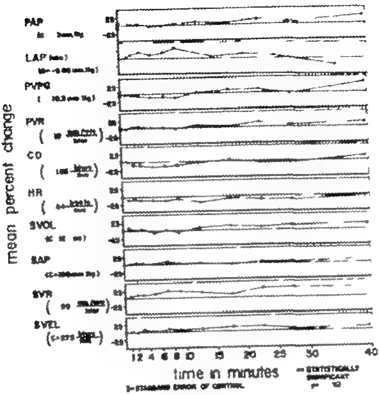

Fig. 4. Mean per cent changes in hemodynamic parameters (vertical axis) in minutes after injection of digoxin (horizontal axis). Summary of all experiments. The zero line for each parameter represents the mean control level for that measurement. Absolute mean control values are printed at the left of each individual graph. The standard error of control means is indicated by the dark, vertical bar at the left edge of each graph. All values are depicted as percentage change from control except for left atrial pressure which is plotted in absolute change in millimeters of mercury.

Mean changes for the designated time period are indicated by a black dot; those statistically significant at a 5 per cent level are shown by a clear dot. See text (under Methods) for meaning of abbreviation.

and increased dSV/dt persisted throughout the experiment, implying a direct cardiac effect rather than a secondary change related to alterations in rate and cardiac filling. SV elevation seemed inversely related to reduced heart rate. Ouabain caused elevated SAP and SVR for about twice as long as acetyl strophanthidin.

Effects of ouabain were qualitatively similar but quantitatively and chronologically slightly different from those of acetyl strophanthidin. Pulmonary vasoconstriction was less marked and occurred later. Although some effects were seen as early as one minute, ouabain generally showed somewhat later vascular and cardiac changes which persisted longer than with acetyl strophanthidin. Electrocardiographic and gastrointestinal toxicity were generally seen about 10 minutes later than with the faster-acting and shorter duration acetyl strophanthidin.

Digoxin. No consistent pulmonary vascular effects were seen after digoxin administration (Fig. 4). Comparable slight initial decreases in PVPG and flow resulted in unchanged PVR. No late effects were noted.

Heart rate slowed (−11 per cent) by the first minute and stayed below control rates but the decrease was less than for the other digitalis drugs. SVel also increased less. Although SAP increased only slightly, some increase in SVR (+5 to +31 per cent) was noted throughout. Since heart rate decrease was minimal, increased SV was also less with digoxin.

Fig. 5 shows six experiments in six dogs in which acetyl strophanthidin was injected into the pulmonary artery of the anesthetized thoracotomized dog. PAP rises in

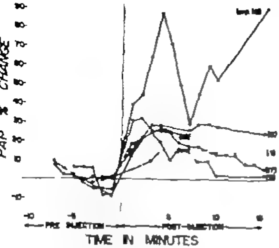

Fig. 5. Effect of acetyl strophanthidin on pulmonary artery pressure in an anesthetized thoracotomized dog with constant pulmonary blood flow and left atrial pressure. Horizontal axis shows pre-injection control period to the left of the zero time line (vertical line) and post-injection values to the right. Horizontal line at zero vertical axis indicates the mean control level with control values of PAP ranging within 10 per cent of the mean. Graph shows all six experiments in which left atrial pressure was kept within 1 mm. Hg of its control level. In all six dogs, pulmonary artery pressure rose after acetyl strophanthidin infusion. Since all other pressures and flows were maintained constant, this indicates pulmonary vasoconstriction.

every case (+10 to +90 per cent). Since pulmonary blood flow and left atrial pressure were constant, this pressure rise parallels a rise in pulmonary vascular resistance. Data was excluded if left atrial pressure increased or decreased more than 1 mm. Hg from control levels.

Discussion

The cardiac and systemic effects of all three digitalizing agents were similar and in agreement with previous reports[1] except that cardiac output showed only a minimal and transient fall (lasting less than 3 minutes for acetyl strophanthidin and ouabain) in our experiments in contrast to reports of a marked fall in cardiac output in the normal subject without heart failure.[11] However, many of these experiments were performed on anesthetized dogs, occasionally with the additional physiological insult of thoracotomy, factors which may have interfered with integrity of reflexes, cardiac dynamics, and vascular reactivity.

In our dogs with normal pulmonary blood flow and no evidence of congestive heart failure, no premedication or anesthesia was given and cardiac output remained relatively constant after administration of cardiac glycosides.

All changes were less marked with digoxin than with acetyl strophanthidin or ouabain. Some effects were seen as early as one minute, but it is possible that a longer time period for the pulmonary vascular action of digoxin may have masked a slight pulmonary vasoconstrictive effect occurring at varying times in each experiment. On the other hand, digoxin is chemically different from the strophanthidins and its effects may be different pharmacologically as well as chronologically. Another difficulty was that most experiments were terminated at about 40 minutes because of the onset of ventricular ectopic beats, nausea, or vomiting. In view of the lag in action of ouabain as compared to acetyl strophanthidin, the slower acting digoxin might have shown similar effects if the animals could have been monitored for extended periods of time. Although not shown in Fig. 3, a small number of observations resulted in a statistically significant increase in PVR 50 minutes after digoxin administration and increase in SV was significant for a small number of observations at 70 minutes, lending some support to the possibility of delayed digoxin action.

Sonnenblick and associates[12] have recently demonstrated that the acceleration of blood flow during early ventricular ejection as recorded by the electromagnetic flowmeter provides an estimate of change in myocardial contractility, paralleling the measurement of rate of rise of ventricular pressure (dP/dt). In our experiments increased peak S Vel after administration of cardiac glycosides conformed with reported measures of myocardial contractility.[13] The first derivative of the rise in S Vel, which reflects the acceleration of blood into the aorta immediately after the opening of the aortic valve, showed a similar rise following glycoside administration, exclusive of rate change and in the face of increased SVR.

Systemic vascular constriction was seen with all three drugs in agreement with previous reports.[14]

Only a limited number of studies have been made concerning the pharmacological effects of digitalis glycosides on the pulmonary circulation. The present study is the first in which cardiac output and pulmonary vascular pressures were measured after digitalis administration in the intact unanesthetized unsedated dog. Macht showed that pulmonary artery branches of the pig and cow constricted after direct application of various digitalis preparations. Kim and Aviado[17] found that acetyl strophanthidin caused an increase in calculated pulmonary vascular resistance in the anesthetized thoracotomized dog. Subsequent experiments ruled out the possibility that this increase in calculated resistance represented a passive response secondary to a reduction in pulmonary blood flow. Complete perfusion experiments established the local vasoconstrictor action of acetyl strophanthidin in their preparation.[18]

In Kim and Aviado's experiments,[17] as in ours, an increase in pulmonary vascular resistance induced by a local vascular action of acetyl strophanthidin could not have been assumed even if pulmonary artery pressure increased, unless blood flow was maintained constant. In other reports, apparent increases in PVR following digitalis administration could have been related to decreased pulmonary blood flow. In our experiments on the intact unsedated dog, a steady state prevailed with fairly constant cardiac output and pulmonary blood flow throughout all experiments so that the rise in pulmonary vascular resistance can be ascribed to pulmonary vasoconstriction.

Since digitalis drugs affect the left heart there is a possibility that the rise in PVPG and PVR might have been due to a fall in left atrial pressure and passive collapse of some pulmonary veins. Figs. 1 and 2 indeed show a fall in left atrial pressure following digitalis administration. However, if the rise in PVR was due primarily to pulmonary vein collapse secondary to decreased left atrial distending pressure we would expect PAP to fall an equivalent amount or to stay at about the same level. On the contrary, PAP was elevated during the first 12 minutes after acetyl strophanthidin administration and for 20 minutes after ouabain administration, suggesting that true vasoconstriction had occurred.

PAP rose in every instance following injection of acetyl strophanthidin in the anesthetized thoracotomized dog with constant pulmonary blood flow and left atrial pressure (Fig. 5). Although this preparation is far different from the intact unanesthetized dog, similar pulmonary circulatory changes occur, tending to eliminate altered left or right heart dynamics as primary mechanisms for the apparent pulmonary vasoconstriction produced by cardiac glycosides. In this preparation, fixed pump rate and flow eliminated any possible effects on the pulmonary circulation of altered right ventricular output, rate, or contractility. Compared to the perfusion experiments of Kim and Aviado,[17,18] our preparation caused less interference with neurological and humoral factors.

We cannot predict whether the human pulmonary vascular bed is equally reactive to the cardiac glycosides or whether actions are modified in the presence of altered flow conditions and anatomical derangements. Furthermore, alterations in time of maximal effect and slower action following oral or intramuscular administration may obscure the pulmonary vasoconstrictive effects of cardiac glycosides observed in our experiments. Although previous studies suggested that hepatic venoconstriction caused decreased cardiac output in normal dogs, this was not seen in these intact unsedated unanesthetized animals. However, since other cardiovascular effects of digitalis drugs are similar in dog and man, our experimental findings concerned with the pulmonary circulation may have clinical pertinence.

REFERENCES

1. Dock, W., and Tainter, M. L.: The circulatory changes after full therapeutic doses of digitalis, with a critical discussion of views on cardiac output, J. Clin. Invest. 8:467, 1930.
2. Cotten, M. deV., and Stopp, P. E.: The action of digitalis on the nonfailing heart of the dog, Am. J. Physiol. 192:114, 1958.
3. Braunwald, E., Bloodwell, R. D., Goldberg, L. I., and Morrow, A. G.: Studies on digitalis. IV. Observations in man on the effects of digitalis preparations on the contractility of the nonfailing heart and on total vascular resistance, J. Clin. Invest. 40:52, 1961.
4. Friedberg, L., Katz, L. N., and Steinitz, F. S.: The effect of drugs on the pulmonary and sys-

temic arterial pressures in the trained unanesthetized dog, J Pharmacol & Exper Therap. 77:80, 1943
5. Fowler N O Effects of pharmacologic agents on the pulmonary circulation, Am. J Med. 28:927 1960.
6. Aviado, D M The pharmacology of the pulmonary circulation, Pharmacol Rev 12:159 1960.
7. Rudolph A M and Paul, M H Chronic catheterization of the pulmonary and systemic circulation A technique for repeated measurements of cardiac output and pulmonary and systemic pressures in the unanesthetized dog, J Appl. Physiol. 10:327 1957
8. Waldhausen, J A Kilman, J W Herendeen, T L. and Abel, F L. Effects of acetylstrophanthidin on coronary vascular resistance and myocardial oxygen consumption, Circulation Res. 16:203 1965
9. Dixon, W J and Massey F J Jr Introduction to statistical analysis, New York, 1957 McGraw Hill Book Co Inc., p. 115
10. Mason D The cardiovascular effects of digitalis in normal man Clin. Pharmacol. Therap. 1 1966.
11. Selzer A and Kelly J J J Action of digitalis upon the nonfailing heart A critical review Progr Cardiovas. Dis. 7:273, 1964
12. Sonnenblick, E. H. Ross, J J Covell J W Kaiser G A., and Braunwald, E.: Velocity of contraction as a determinant of myocardial oxygen consumption, Am. J Physiol. 209:919 1965
13. Gleason, W L., and Braunwald, E. Studies on the first derivative of the ventricular pressure pulse in man, J Clin. Invest. 41:80, 1962.
14. Walton R. P and Gazes, P C. The effect of digitalis and other drugs on heart contractile force clinical implications, South M J 44:418, 1951
15. Ross, J J Braunwald, E., and Waldhausen, J A. Studies on digitalis. II Extracardiac effects on venous return and on the capacity of the peripheral vascular bed, J Clin. Invest. 39:937 1960.
16. Macht, D I The action of drugs on the isolated pulmonary artery J Pharmacol. & Exper Therap 6 13 1914
17. Kim, Y S., and Aviado, D M Digitalis and the pulmonary circulation, Am. Heart J 62:680, 1961
18. Aviado, D M The lung circulation, Vol. II. New York, 1965 Pergamon Press, Inc., p 638

Relative effectiveness of antiarrhythmic drugs in treatment of digitalis-induced ventricular tachycardia

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The management of digitalis-induced cardiac arrhythmias remains a common clinical problem in which the relative usefulness of the available therapeutic agents is not established. A previous study of the effects of several antiarrhythmic drugs on the ventricular tachycardia produced by ouabain was limited by the fact that the criterion for restoration of normal sinus rhythm was limited to two minutes[1] and did not account for the possible transient nature of the response.

The purpose of this study was to compare the transient and/or persistent effectiveness of these compounds as antiarrhythmic agents, their relative side effects, and their influence on the inotropic effect of digitalis. Since the intravenous route of administration remains more appropriate in the presence of serious ventricular tachycardias, an agent with potentially profound depressant effects on the cardiovascular system (which large doses of quinidine exhibit) is undesirable. Less severe effects may be anticipated in the case of drugs related to the local anesthetic group, procaineamide and lidocaine. These have been compared with anticonvulsant Dilantin[2] and the recently introduced propranolol with its mixed properties as an analgesic and β-receptor inhibitor. It has been assumed that the most desirable therapeutic agent would produce a sustained restoration of normal sinus rhythm associated with minimal circulatory depression.

Methods

Adult male mongrel dogs in good health, weighing between 15 and 25 kilograms were used for these experiments. To exclude the possible influence of anemia and hypokalemia, only animals with normal hematocrits and serum potassium were studied. They were premedicated with 3 mg. per kilogram of morphine sulfate intramuscularly and anesthetized with 12 mg. per kilogram of pentobarbital sodium intravenously. The trachea was intubated with a cuffed endotracheal tube and ventilation was maintained with a Harvard respiratory pump. Arterial blood oxygen saturation and pH were maintained within normal limits by monitoring on a Beckman DU

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spectrophotometer and Beckman pH meter at 37° C. The occasional desaturated animal was ventilated on 100 per cent oxygen.

An empirical relationship between left ventricular end-diastolic pressure (LVEDP) and the maximum rate of pressure rise (dp/dt) has been suggested as an index of ventricular contractility[6] and has been chosen as a feasible means of evaluating this parameter in experiments of many hours' duration in the intact dog. In all studies of animals not subjected to inotropic intervention a good correlation between these two parameters has been observed while aortic pressure and heart rate are unaltered.[7] When cardiac contractility is directly increased by a cardiac glycoside the maximum rate of pressure development is enhanced without a rise in filling pressure.[7]

Left ventricular pressures were measured through a 50 cm. No. 8 Goodale-Lubin catheter introduced retrograde into the left ventricle from the left carotid artery and connected directly to a Statham C 23Db strain gauge transducer. The left ventricular systolic and end-diastolic pressure, its first derivative (dp/dt) and the standard Lead II electrocardiogram (ECG) were monitored continuously on an oscilloscope and recorded intermittently on a multichannel Electronics for Medicine amplifier-recorder system. The first derivative of left ventricular pressure (dp/dt) was obtained from an R-C differentiating circuit. Changes in the maximum of the first derivative were expressed as per cent of control.

All dogs were made digitalis-toxic by infusing a dose of Cedilanid that is usually not lethal (0.15 mg. per kilogram) over 1 minute,[8] through a catheter placed in the superior vena cava for administration of drugs. Six control animals received only Cedilanid and were followed for the 3 to 4 hour duration of the ventricular tachycardia using accepted criteria for this arrhythmia.[9] The other animals were divided into four therapeutic groups. Treatment was initiated 15 to 45 minutes after the onset of a ventricular arrhythmia and the drug was infused over 1 minute. If there was no response or if the arrhythmia reappeared within 30 minutes, total drug dosage was increased by repeating the initial dose until normal sinus rhythm (NSR) was maintained for at least 30 minutes or until ventricular systolic pressure was reduced a *maximum of 5 to 10 mm. Hg*. In this case subsequent doses were delayed until blood pressure was restored to virtually control values. Further doses were given to a maximum of eight in a period of not longer than 2 hours. This would ensure that the disappearance of the ventricular tachycardia was not due to the spontaneous disappearance of the Cedilanid effect, since the glycoside-induced tachycardia persisted for at least 3 hours.

A total of 13 animals received propranolol (Inderal), an average total dose of 1.6 mg. per kilogram intravenously, each dose equal to 0.4 mg. per kilogram.

Eight animals received procainamide hydrochloride (Pronestyl), an average total dose of 30 mg. per kilogram intravenously in divided doses of 10 mg. per kilogram.

Seven animals received diphenylhydantoin sodium (Dilantin), an average total dose of 15 mg. per kilogram intravenously in divided doses of 5 mg. per kilogram.

Seven animals received lidocaine (Xylocaine), an average total dose of 12 mg. per kilogram intravenously, in divided doses of 3 mg. per kilogram.

Results

Ventricular tachycardia appeared within 5 to 30 minutes after the administration of Cedilanid. This arrhythmia persisted for at least 3 hours in the control animals receiv-

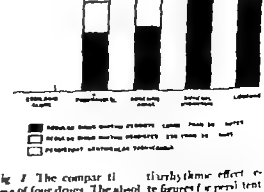

Fig. 1. The comparative antiarrhythmic effectiveness of four drugs. The absolute figures for per cent restoration of NSR in the box groups from left to right were, 6 of 13, 4 of 8, 6 of 7, and 5 of 7.

ing no antiarrhythmic drug without the appearance of normal sinus beats. Fig 1 summarizes the appraisal of the four drugs which was performed within the 3 hour period when Cedilanid toxicity was expected to persist

Propranolol abolished the arrhythmia for a persistent period in 6 of 13 dogs. In three additional animals, the restoration of sinus rhythm lasted for less than 30 minutes. The arrhythmia was entirely resistant to propranolol in four animals treated with maximal doses which significantly reduced arterial pressure.

Procaineamide abolished the ventricular tachycardia in four of eight dogs. In an additional three animals the NSR was maintained for less than 30 minutes despite repeated dosages. One of the three dogs died of complete A V block 1 hour after the administration of procaineamide In the eighth animal the arrhythmia was partially converted to NSR with many premature ventricular contractions.

Dilantin converted the ventricular tachycardia to NSR in all seven dogs. In all except one, the sinus rhythm was maintained until the end of the observation period of at least 60 minutes. The one animal with recurrent episodes of tachycardia failed to maintain sinus rhythm despite repeated doses of Dilantin

Lidocaine converted the ventricular tachycardia to NSR in all seven dogs, which persisted through a 60 minute period of observation in five animals, but was never longer than 30 minutes in two. One animal exhibited transient first degree A V block and another developed asystole then complete A V dissociation which

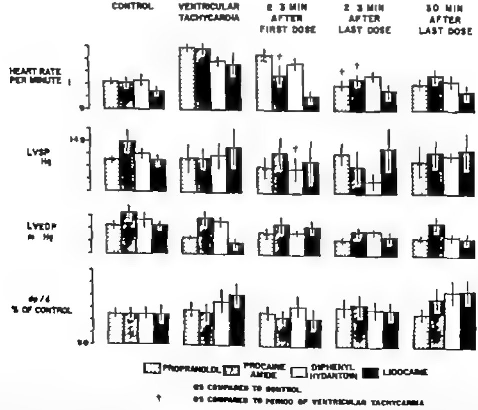

Fig Hemodynamic responses to the antiarrhythmic drugs during Cedilanid-induced ventricular tachycardia. Control values were obtained before the glycoside was administered, and the data during ventricular tachycardia were obtained prior to giving the antiarrhythmic agent Measurements of hemodynamic parameters at 2 to 3 minutes and at 30 minutes after the last dose of antiarrhythmic drug were done only during periods of normal sinus rhythm. In the last period when the arterial pressure and heart rate were at control levels, the positive inotropic response to Cedilanid was evident in the Dilantin and lidocaine groups.

evolved into ventricular tachycardia followed by sinus rhythm.

In all four groups successful restoration of regular sinus rhythm occurred within 30 to 90 seconds after the intravenous administration of the antiarrhythmic agent. This response time did not, however, distinguish a transient from persistent restoration of NSR.

The most notable hemodynamic effect of these drugs was to reduce cardiac rate from that existing during toxicity, readily seen after the last therapeutic dose (Fig. 2). Systemic arterial pressure was reduced by procaineamide and Dilantin, most evident immediately after the last intervention. The interaction of the antiarrhythmic compounds and Cedilanid on left ventricular dp/dt was most readily judged 30 minutes after the last dose of the antiarrhythmic agent when heart rate and systemic arterial pressure did not significantly differ from control. It is noteworthy that after the last dosage both the Dilantin and lidocaine groups exhibited a significantly enhanced left ventricular dp/dt over the control period. This was associated with a small, non-significant reduction of filling pressure.

Discussion

This comparison of antiarrhythmic drugs was performed at dose levels which are depressant to the cardiovascular system when these agents are used alone,[2-4] so that by this standard an approximation has been made to equivalent dosages in this study.

Data from animal studies indicate that depression of circulatory function is related to the dose and rate of administration of the antiarrhythmic drugs when given alone. While this study does not establish the optimal dose or rate of administration, it is possible that the dose at which the therapeutic effect is operative against a fully established and persistent ventricular tachycardia approximates the dosage at which some evidence of circulatory depression is seen in the normal undigitalized animal.[3] Lesser degrees of digitalis toxicity manifest as isolated ventricular ectopic beats or as a bigeminal rhythm may be responsive to lower doses. As a corollary to this view, the arrhythmia that is less difficult to manage may be highly responsive to agents of lesser effectiveness in this study, propranolol and procaineamide.

It is noteworthy that depression of circulatory function by antiarrhythmic agents in animals treated with Cedilanid was less than has been observed in the undigitalized dog.[2-4] Since many animals exhibited neither a decline of systemic arterial pressure or left ventricular dp/dt while converting to normal sinus rhythm, depression of circulatory function to below control levels would not appear to be essential for the antiarrhythmic effect. After the sinus rhythm was re-established the positive inotropic effect of Cedilanid was at least partially evident in the animals treated with Dilantin and lidocaine. Since this property of the glycoside may be attenuated by Nembutal anesthesia, a qualitatively similar effect in animals treated with propranolol or procaineamide might be observed in the absence of the barbiturate.

This study has indicated that Dilantin and lidocaine appear to be the most useful of the agents tested for conversion of ventricular tachycardia due to digitalis intoxication to normal sinus rhythm. Unanticipated problems, however, may occur with these compounds in situations of clinical disease. It is known that effectiveness of at least some of these agents is altered by abnormalities of blood pH or potassium concentration.[10] A compound whose activity is minimally altered by these circumstances would have obvious merit. It would seem probable from these animal studies that in the clinical setting of reduced arterial pressure, lidocaine would be preferable since this compound had a minimal effect on systemic arterial pressure. However, in the presence of a conduction delay in the myocardium exhibiting a ventricular tachycardia due to digitalis excess, Dilantin would seem to be the more useful agent, since conduction delays seen after procaineamide and lidocaine were not encountered after Dilantin. This is supported by a previous report indicating that the latter drug does not prolong atrioventricular or intraventricular conduction times.[11,12]

The mechanism of action of th anti-

arrhythmic agents is not established. While there may be differences in the mode of action of these drugs a mechanism involving the regulation of potassium release from the myocardium has been invoked for procaineamide in the presence of ventricular arrhythmias due to acetylstrophanthidin.[13] This drug has been found to reduce the myocardial egress of potassium due to toxic doses of digitalis, associated with maintenance of normal sinus rhythm. A similar relationship has been observed during arrhythmias related to other causes[13] supporting the view that control of ion transport is crucial to the elimination of ventricular ectopic foci.

Summary

This study was designed to compare the transient and persistent effectiveness of our antiarrhythmic agents, their relative side effects, and influence on the inotropic effect of digitalis. Ventricular tachycardia was induced in the intact anesthetized dog using 50 per cent of the lethal dose of Cedilanid. Six control animals receiving Cedilanid alone were found to have a sustained ventricular tachycardia for at least 3 hours.

All four drugs were administered at doses depressant to circulatory function. Propranolol and procaineamide treatment groups were found to have a sustained antiarrhythmic effect in slightly less than 50 per cent of the animals. Animals entirely resistant to drug therapy were found in both the propranolol and procaineamide treatment groups. Dilantin and lidocaine restored sinus rhythm in all animals and the normal rhythm was maintained in the majority. Of the latter two agents, Dilantin had a greater tendency to reduce arterial pressure and lidocaine was associated with conduction delays.

With the restoration of normal sinus rhythm in the latter two groups a positive inotropic response to Cedilanid was found to be present. It was suggested that the latter two agents would appear to offer therapeutic advantages in the presence of a sustained ventricular tachycardia due to digitalis excess.

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REFERENCES

1. Mosey, L., and Tyler, M. D.: Effect of diphenylhydantoin sodium (Dilantin), procaine hydrochloride, procaine amide hydrochloride, and quinidine hydrochloride upon ouabain-induced ventricular tachycardia in unanesthetized dogs, Circulation 10:65, 1954.
2. Austen, W. G., and Moran, J. M.: Cardiac and peripheral vascular effects of lidocaine and procaine amide, Am. J. Cardiol. 16:701, 1965.
3. Mixter, C. G., III, Moran, J. M., and Austen, W. G.: Cardiac and peripheral vascular effects of diphenylhydantoin sodium, Am. J. Cardiol. 17:332, 1966.
4. Shanks, R. G.: The pharmacology of B sympathetic blockade, Am. J. Cardiol. 18:308, 1966.
5. Reeves, T. J., Hefner, L. L., Jones, W. B., Coghlan, C., Prieto, G., and Carroll, J.: The hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction, Am. Heart J. 60:745, 1960.
6. Siegel, J. H., and Sonnenblick, E. H.: Isometric time-tension relationships as an index of myocardial contractility, Circulation Res. 12:597, 1963.
7. Wallace, A. C., Skinner, N. S., and Mitchell, J. H.: Hemodynamic determinants of the maximal rate of rise of left ventricular pressure, Am. J. Physiol. 205:30, 1963.
8. Burcher, R. P., and Jabbur, S. J.: Toxic effects of cardiac glycosides and antidotal effects of different compounds in the cat, Fed. Proc. 15:282, 1955.
9. Katz, L. N., and Pick, A.: Clinical electrocardiography. The arrhythmias, Philadelphia, 1956, Lea & Febiger Publishers, p. 290.
10. Dreifus, L. S., Robbino, M. D., and Watanabe, Y.: Newer agents in treatment of cardiac arrhythmias, M. Clin. North America 48:371, 1964.
11. Helfant, R. H., Scherlag, B. J., and Damato, A.: The electrophysiological properties of diphenylhydantoin sodium as compared to procaine amide in the normal and digitalis-intoxicated heart, Circulation 36:108, 1967.
12. Helfant, R. H., Scherlag, B., and Damato, A.: Protection from digitalis toxicity with the prophylactic use of diphenylhydantoin sodium. An arrhythmic-inotropic dissociation, Circulation 36:119, 1967.
13. Regan, T. J., Harman, M. A., Lehan, P. H., Burke, W. M., and Oldewurtel, H. A.: Ventricular arrhythmias and K transfer during myocardial ischemia and intervention with procaine amide, insulin, or glucose solution, J. Clin. Invest. 46:1657, 1967.

The effect of age and athletic training on the maximal heart rate during muscular exercise

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The maximal heart rate possible during the most severe muscular exercise is known to decline with age It has been clearly established that the heart rate of a group of trained athletes will be lower at rest and during any given level of submaximal exercise than the heart rate of untrained persons.[4] However the effect of physical training on the maximal heart rate possible during maximal exercise is not clear

Taylor and co-workers, Andersen and associates, and Bruce and colleagues have stated that there is a definite decrease in the maximal heart rate of young trained athletes. The evidence supporting this belief is not impressive Many investigators have shown in individual young athletes, maximal heart rates in excess of 190 to 200 beats per minute[12,1] Astrand has stated that there was no significant difference between the maximal heart rates of trained and untrained subjects. Studies of two groups of trained athletes aged 20 to 30 years have revealed mean maximal heart rates of 194 and 195 beats per minute respectively[12,1] Benestad[1] found no decrease of the maximal heart rate in subjects aged 71 to 80 years who undertook a supervised program of training Recently Grimby and Saltin measured the maximal heart rates of 33 athletes (ages 42 to 68) more than one half of these exceeded the predicted mean maximal heart rate for untrained individual of the same age as described by Robinson[1] and two thirds exceeded similar standards reported by Astrand

This question has recently assumed a measure of clinical importance Sheffield and associates[19] have developed a submaximal exercise electrocardiographic test based on the predictability of the maximal heart rate as a function of age Although other variables have been controlled no correction has been made for the state of athletic training The end point of the test is taken to be a heart rate 85 per cent of the maximal predicted for age If athletic training materially lowers the maximal

With the statistical collaboration of David Hurst, Ph D
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heart rates, it is obvious that such a test imposes a greater relative circulatory stress on those in athletic training. The present study was designed to compare the maximal heart rates of trained and untrained subjects over a wide range of age during graded, uninterrupted treadmill exercise.

Methods

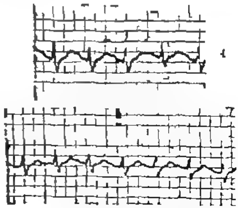
Heart rates were measured during maximal treadmill exercise in 190 male volunteers, ages 15 to 75, from local high schools, colleges, Young Men's Christian Associations (YMCA), and fire departments, and also business and professional men from the Birmingham area. A total of 108 of these subjects were also volunteers for a study of electrocardiographic response to maximal exercise.[22] Any subject with evidence of hypertension or heart disease by history or physical examination was excluded from this study.

The exercise habits of all subjects were carefully noted. A total of 148 subjects (mean age 42.73) whose activities were limited to golf, walking, occasional tennis, or less strenuous sports were classified as nontrained. None of the individuals so classified in the younger age group had participated in high school or college varsity athletics in the three years prior to testing. A total of 42 subjects (mean age 30.24) were classified as trained athletes. This group included 8 members of the Alabama state championship high school track team, 13 members of the University of Alabama cross-country track team, one 4-year-old 1964 Olympic hurdler still in active training, one 32-year-old Olympic athlete (current Kansas Relay Decathlon Champion), and 18 volunteers from the YMCA who ran from 4 to 11 miles daily. One championship class weight lifter, 50 years of age, was included in this group, although the physiological difference of this type of training was recognized. Table I illustrates the number of volunteers per decade in each group.

The same physician and technician were in attendance for all tests, which were conducted in an air-conditioned room with an ambient temperature of 71° F. ± 2 degrees. All subjects were studied in the fasting state. Precautions previously described to insure the safety of the volunteer were taken.[22] Electrocardiographic monitoring of rate and rhythm during exercise was accomplished by means of a telemetry system employing a bi-polar lead from the right scapula to the V position yielding a tracing similar to the standard V lead. This lead was recorded in every case on the same Sanborn 100 recorder at a chart speed of 50 mm. per second (speed verified at ± 0.25 mm. per second). From the tracings made during the last 30 seconds of exercise, maximal heart rate determinations were made. Fig. 1 illustrates the technical quality of the records which bears on the precision with which the heart rates could be measured with the recording system used.

Table I. Number of volunteers per decade in the untrained and trained groups

Group by age	No. of volunteers		
	Untrained	*Trained*	*Total*
10–19	22	14	36
20–29	7	6	13
30–39	13	8	21
40–49	52	6	58
50–59	38	6	44
60+	16	2	18



A

B

Fig. 1. Representative electrocardiographic tracings obtained during maximal exercise with corresponding determined maximal heart rate. Paper chart, speed 50 mm. per second. *A*, Maximum heart rate, 173. *B*, maximum heart rate, 188.

A total of 143 subjects carried out a maximal multistaged uninterrupted treadmill test the duration of each stage being three minutes. The speed and grade of elevation of the treadmill used in this test was identical to that utilized by Doan and associates.[22] Forty-six subjects (24 nontrained and 22 trained) from the various high school and college groups underwent a slightly modified version of this test. These volunteers exercised for three minutes at a low level warm up stage and then at the treadmill speed and grade of stage 7 without the intervening stages. The latter work level was maintained until the subjects were exhausted. Previous studies in our laboratory have shown that the maximal heart rates achieved by young normal subjects will be identical with these two modes of testing.

The nature of the test was carefully explained to each participant including the safety precautions available in the laboratory. All subjects aged 45 years and older had a prior negative graded exercise electrocardiographic test as described by Sheffield and colleagues.[23] The subjects were told that unless they developed chest pain or the examiner detected electrocardiographic abnormalities they were to exercise as long as possible." All subjects were cooperative and in most cases distinctly competitive. This was especially marked among the trained group. The exercise was terminated when the individuals were unable or unwilling to continue, usually because of profound dyspnea weakness, or both.

Results

All subjects completed the test to the satisfaction of the examiner and no subject was stopped except at his own request. A cool clammy skin profound dyspnea and obvious pallor were observed in almost every individual and were accepted as an indication that he had reached maximal tolerance. No serious complications were noticed in the subjects included in the study although atrial and ventricular extrasystoles were common in the post exercise period. One subject developed

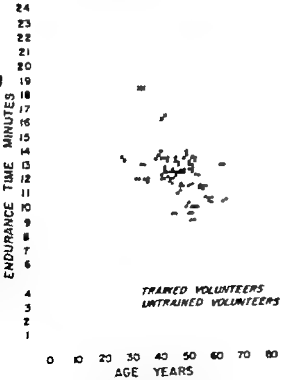


Fig. 2. Duration of treadmill exercise tolerated by 20 trained (T) and 123 untrained ( ) men utilizing the standard multistaged exercise test described by Doan and associates.[22]

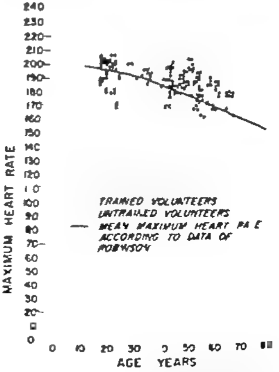


Fig. 3. Maximal heart rat ttained during th la t 30 second of the exercise test i lation t the age of the subject ompared ith the ... of Robinson.

ischemic" (segmental) depression of the ST portion of the electrocardiogram (ECG) during the postexercise period. Five additional subjects had such changes during or immediately after exercise. Occurrence of PVC's in runs of two to three beats either during or after exercise were seen in only two people, both over the age of 60 years. A number of subjects complained of protracted fatigue and two individuals experienced symptoms of postexertional hypotension. None complained of chest pain.

Fig. 2 illustrates the duration of treadmill testing required to produce maximal exercise tolerance for 143 individuals (20 trained and 123 untrained) tested with the standard multistaged exercise test described by Doan and associates.[22] A clear separation is seen between the two groups with minimal overlap. The two individuals (who are brothers) classified as untrained who had a 19.0 and a 15.7 minute treadmill test time were ardent tennis players, and played several sets of singles tennis three times per week. In retrospect it seems likely that these subjects should have been classified as trained athletes. Although the trained group was younger, it is clear from an inspection of this figure that at any given age the athletes had longer times on the treadmill and performed more work.

The maximal heart rate attained during the last 30 seconds of the exercise test with relation to the age of the subject is illustrated in Fig. 3. The responses of the trained and the untrained subjects are compared to each other and to the older observations of Robinson. Though there was significant overlap between the two groups, there was a tendency for the trained subjects at any given age to have a lower maximal heart rate than the sedentary individuals did. The untrained group (84 per cent) and the trained group (54 per cent) attained a heart rate greater than the mean maximal heart rate reported by Robinson for subjects of the same age.

There was a significant negative correlation ($p < 0.01$) between the ages of subjects and the maximal heart rate attained during exercise (Fig. 4). For the

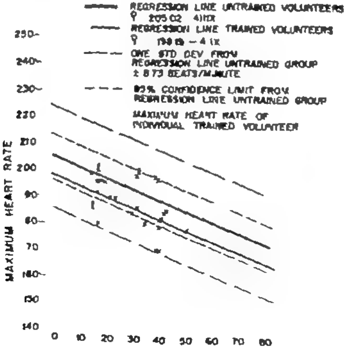


Fig. 4. The maximal heart rates of the trained subjects are shown in relation to the regression line, standard deviation, and 95 per cent confidence limit of the data from the untrained volunteers.

trained group the coefficient of correlation was −0.541 and the linear regression equation was $\hat{Y}_T = 196.77 - 0.346x$. For the untrained group the correlation was 0.578 and the equation was $\hat{Y}_U = 205.62 - 0.425x$. The influence of weight, height, and body surface area on the relationship of maximal heart rate to age was examined by a multiple linear stepwise regression analysis. No significant increase in the correlation of age to maximal heart rate was found when these additional variables were added to the analysis either individually or together

The next statistical hypothesis tested was the equality of the two regression lines describing the trained and untrained subjects i.e. considering both intercepts and both slopes simultaneously was there evidence of two different regression lines? The F value for this test was 37.30 which is significant at $P < 0.01$ with 2 and 185 degrees of freedom. Thus the two lines were different in some respects.

The final test was the hypothesis of equal slopes i.e. considering the intercepts different was there evidence of different slopes? The F value was 0.34 with 1 and 185 degrees of freedom indicating no difference of slope. Thus we were left with the conclusion of parallel lines as follows

$$\hat{Y} = 198.19 - 0.411$$

$$\hat{Y} = 203.02 - 0.411$$

and we had the trained subjects showing a significant over-all difference in maximal heart rate of 0.83 beats per minute but declining with age at the same rate as the untrained subjects, i.e. 0.411 beats per year of age.

One standard deviation from the regression line for the untrained group is ± 8.73 beats per minute. As can be seen in Fig. 4 the regression line for the trained group (single unbroken line) actually falls within this value. In addition all but two of the trained individuals fall within the 95 per cent confidence limits (± 19.4 beats per minute) established from the regression line of the untrained subjects.

Discussion

From the analysis of these data four conclusions may be made (1) The maximal heart rate of trained athletes during treadmill exercise of the type employed in this study was slightly but significantly lower than that of more sedentary individuals. This finding is constant for all age groups. (2) Although two regression lines are necessary to satisfy the analysis of the data the normal heart rate of a trained athlete would be expected to fall within the 95 per cent confidence limits of the regression line of the untrained subjects. (3) There was a significant negative correlation between the age of the subject and the maximal heart rate attained during exercise in both trained and untrained groups. (4) Neither the height nor weight of the individuals tested had a significant effect on their maximal heart rate

The mean maximal heart rate for the untrained group was somewhat higher than the values reported by Robinson.[1] This is particularly evident among individuals over 50 years of age. The enthusiasm spirit of competition and over all general health exhibited by the volunteers of this study probably were higher than those of the PWA volunteers of 1938.[1] It is also known that the average size and life span of the American male have increased significantly over the last 25 years. Whether there is a corresponding increase of athletic performance and/or in maximal heart rate is open to question. The last and probably the most important reason is the much larger sample of healthy older men (over 50) available for testing

Crumby and associates[18] have shown a significant direct relationship of the resting pulse and the maximal heart rate ($r = 0.81$) even though the resting pulse decreases during training. The findings of this study were consistent with those observations. The regression lines of the trained and the untrained groups had an identical slope and were different only in intercept. It is well known that the resting pulse of the athlete is less than that of more sedentary persons

The mechanism of the decrease in the maximal heart rate of the athlete is not clear. The method of testing (continuous treadmill exercise with elevation) was unfamiliar to both groups. However leg discomfort was a common complaint in the athlete. Many of these individual felt that the marked leg discomfort con

tributed to their decision to terminate exercise. Much of training is repetition and accustoming oneself to endure discomfort.[23] Thus continuous run uphill may have caused more leg discomfort relative to dyspnea and exhaustion in the athletes than in the untrained subjects. Thus, one might consider the decision to terminate exercise as the sum of several factors, including leg discomfort, dyspnea and fatigue, or weakness, these modified by the motivation to continue. It is at least possible that the relative proportion of the noncirculatory components of this decision was greater in the athletes, such that the stimulus to the sinoatrial node was less in these subjects than in the more sedentary individuals.

There is a definite question as to whether an athlete is born or made. There is some evidence that the former is the case. Sexton[24] reported a study of some 150 subjects who were tested twice a year beginning at age 7 and continuing for as long as 13 years. Values obtained for maximal oxygen intake were arranged in percentiles. Most of the subjects (75 per cent) remained in the same percentile with very little variation regardless of activity over the years. Taylor and Grande[25] reported that many highly trained athletes do not increase their maximal oxygen intake after they have reached their full growth. Likewise, no significant evidence has been presented that continuing rigid physical training will result in an improvement of maximal oxygen intake. Many athletes continue to maintain maximal oxygen intake values similar to those of their trained status long after they stop all regular physical training. Sedentary offspring of athletes have frequently demonstrated a value similar to the parent's. The possibility that an individual inherits a maximal heart rate is an enticing thought but is speculation.

A neurohumeral mechanism for the reduction in maximal heart rate is possible. The increased vagal tone exhibited by the athlete could contribute to the observed diminution of the maximal heart rate. Atropine, however, administered to the untrained subject does not alter the maximal heart rate.[26] There is indirect evidence[27] that athletic training decreases myocardial catecholamine concentrations. It is known that β-adrenergic blocking compounds decrease heart rates at all levels of exercise, as well as other indices of cardiac function.[28] The relevance of these observations to the question is admittedly unclear. They do however suggest possible avenues of experimentation that might provide additional insight into this mechanism.

Although the athlete's mean maximal heart rate is lower than that of the untrained subject, the difference is small and there is marked overlap. As already pointed out, the heart rate of an athlete would be expected to fall within two standard deviations of the predicted mean value for the untrained group. The heart rate levels required by Sheffield and colleagues[29] for the Graded Exercise Test (85 per cent of the predicted maximal value) are below the 95 per cent confidence limits of the regression line for the untrained group of the present study. Therefore, the GXT would have been a submaximal test for all normal males in the present study, including the athletes. It is evident, however, that the test easily could be refined by taking the difference in maximal heart rates into account.

The decline of the maximal heart rate with increasing age is well known and has again been demonstrated here. The mechanism for this phenomenon is uncertain. Many factors may be involved, including the neurohumeral mechanisms considered in relationship to athletic training, the increased duration of isovolumic relaxation of the older individual,[30] the fear of severe exercise by the older person, and the increased prevalence of peripheral atherosclerosis. It is possible that there is a direct effect of the aging process on the sinoatrial node, decreasing its rhythmicity.

Summary

The maximal heart rate of 190 healthy male subjects was measured during exhausting treadmill exercise. A total of 148 of these men were accustomed to a sedentary or semisedentary life while 48 of them were trained athletes. The influence of age, height, weight, and athletic training on the maximal heart rate was examined.

A highly significant negative correlation was found between the maximal heart rate and the age of the subject. No sig

nificant influence of height or weight on this relationship was detected by a linear multiple stepwise regression analysis. However at any given age the athletes had a slightly but significantly slower maximal heart rate than the untrained men. Thus the regression equations for the two groups MHR (sedentary) = 205 02 − 0 411 age and MHR (athletes) = 198 19 − 0 411 age are significantly different by virtue of differences in the intercept value al*though the slopes of the lines are identical*

From these observations it is apparent that predictions of maximal heart rate could be improved by making a distinction between trained and untrained subjects

REFERENCES

1. Robinson, S Experimental studies of physical fitness in relation to age, Arb Physiol. 10:251 1938.
2. Bruce R. A. Blackmon, J R., Jones, J W and Strait G. Exercising testing in adult normal subjects and cardiac patients, Pediatrics 32 Suppl. 742 1963
3. Astrand, I Aerobic work capacity in men and women with special reference to age, Acta physiol. scandinav (Suppl. 169) 49 1 1960.
4. Strandell, T Heart rate and work load at maximal working intensity in old men Acta med. scandinav 176:301 1964
5. Hanson, J S and Tabakin, B S Comparison of the circulatory response to upright exercise in 25 "normal" men and 9 distance runners, Brit. Heart J 7:211 1965.
6. Cobb, L. A., and Johnson W P Hemodynamic relationships of anaerobic metabolism and plasma free fatty acids during prolonged, strenuous exercise in trained and untrained subjects, J Clin. Invest. 42:800, 1963
7. Grimby G. and Saltin, B. Physiological analysis of physically well trained middle-aged and old athletes, Acta med scandinav 179:513 1966.
8. Grimby G. and Saltin, B. Daily running causing Wenckebach heart-block, Lancet 2:962, 1964
9. Taylor H L., Wang Y Rowell, L and Blomqvist, G. The standardization and interpretation of submaximal and maximal tests of working capacity Pediatrics 32:Suppl. 703, 1963.
10. Andersen, K. L.: Interaction of chronic cold exposure and physical training upon human body tolerance to cold. Report A. F 61 (052)-758, Institute of Work Physiology Oslo, 1964
11. Bruce R. A., Rowell, L. B Blackmon, J R., and Doan, A. Cardiovascular function tests, Heart Bull. 14:9 1965.
12. Robinson, S., Edwards H T and Dill, D B. New records in human power Science 85 409 1937
13. Astrand, P O: A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work, J Appl. Physiol. 7:218, 1954
14. Astrand, P O and Saltin, B Maximal oxygen uptake and heart rate in various types of muscular activity J Appl. Physiol 16:977 1961
15. Astrand, P O Cuddy T E. Saltin, B., and Stenberg, J Cardiac output during submaximal and maximal work, J Appl. Physiol 19:268, 1964.
16. Astrand, P O New record in human power Nature 176:922, 1955
17. Astrand, P O Human physical fitness with special reference to sex and age Physiol. Rev 36:307 1956.
18. Benestad, A. M Trainability of old men, Acta med scandinav 178:321 1965
19. Grimby G and Saltin B Physiological analysis of physically well-trained middle-aged and old athletes, Acta med. scandinav 179:513, 1966.
20. Sheffield, L. T Holt, J H and Reeves, T J Exercise graded by heart rate in electrocardiographic testing for angina pectoris, Circulation 32:622 1965
21. Lester F M Sheffield L. T and Reeves, T J Electrocardiographic changes in clinically normal older men following near maximal and maximal exercise, Circulation 36:5 1967
22. Doan A. E., Peterson, D R Blackmon, J R. and Bruce R. A. Myocardial ischemia after maximal exercise in healthy men method for detecting potential coronary heart disease Am. Heart J 69 11 1965
23. Grande, F and Taylor H L. Adaptive changes in the heart, vessels, and patterns of control under chronically high loads, in Hamilton, W F Handbook of physiology Vol. III Sect. II Baltimore, 1965 The Williams & Wilkins Company p. 2615
24. Sexton, A. W Value of longitudinal studies of exercise fitness tests, Pediatrics 32:Suppl. 730, 1963
25. Robinson, S. Physiology of muscular exercise In Bard, P Medical physiology ed II St. Louis, 1961 The C V Mosby Company p. 494
26. Robinson S. Pearcy F R Brueckman, F R. Nicholas, J R. and Miller D I Effect of atropine on heart rate and oxygen intake in working man J Appl Physiol 5:508, 1953
27. Raab, W and Krzywanek, H. J Cardiovascular sympathetic tone and stress response related to personality pattern and exercise habits a potential cardiac risk and screening test, Am J Cardiol. 16:42 1965
28. Epstein, S. E., Robinson, B. F Kahler R. L and Braunwald E Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man, J Clin. Invest. 44 1745, 1965.
29. Harrison, T R Dixon, K., Russell, R. O Jr Bidwai, P S and Coleman H N: The relation of age to the duration of contraction, ejection and relaxation of the normal human heart Am Heart J 67 189 1964

The electrical impedance cardiogram in health and disease

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This report describes a method of using skin electrodes on the thorax to record electrical impedance changes that reflect continuous changes in heart shape. The electrical impedance of the heart is its opposition (resistance and reactance) to the flow of alternating electrical current This can be measured by passing a radiofrequency current between a pair of electrodes placed on the skin over opposite sides of the heart.

Certain general laws govern the impedance of a volume conductor such as the heart. The impedance of a conductor increases with length and decreases with cross-sectional area. Flattening a balloon full of salt water without changing the amount of contents decreased the impedance across the shortened diameter and increased the impedance across the diameters that increased as compensatory bulges Removing the salt water from the balloon without changing its symmetry increased the impedance across the diameter Impedance increased as the cross-sectional area decreased which was as the square of the radius. This overshadowed the opposing decrease in impedance due to a reduction in length between the electrodes because the length decreased directly with the radius, not with the square of the radius.

Removing blood from the heart increased the impedance measured across the base-to-apex diameter[1] Because of these relationships impedance changes have been used to record cardiac output, blood flows in different parts of the body and changes in electrical impedance of the thorax due to cardiac activity

Various tissues in the thorax influence impedance changes The impedance of the myocardium is five times as great as the impedance of blood Thickening of the myocardium increases impedance Blood ejected into the pulmonary circulation decreases impedance across most diameters of the thorax. Impedance changes along any cardiac axis represent the combined impedance changes of the myocardium the contained blood and the ejected blood These changes, therefore, vary throughout

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the cardiac cycle as the shape of the heart the thickness of the myocardium [6] and the traversed blood volume change

Because so many factors could potentially affect transthoracic impedance it might seem difficult to identify the changes caused by the heart. However the changes caused by the heart stand out. Tracings from normal subjects resemble each other and tracings from patients with known deformities of the heart differ from the normal in a predictable manner

Methods

Changes in impedance of the thorax were detected and converted into an electrical signal by an impedance converter (Biocom Corporation Model 991) This converter powered by a nine volt radio battery generated a 50 kc. alternating current which passed from one electrode through the chest to a second electrode. Such a radiofrequency current is far below the stimulation threshold of living tissue and is therefore entirely innocuous. The converter made a constant voltage changes in impedance were detected as changes in current flow

The signal from the impedance converter was recorded on a variety of instruments, including a direct writing electrocardiograph machine and also a Hart vector cardiograph. Ordinary electrocardiograph electrodes were placed on the skin at opposite sides of the chest. Commonly one electrode was placed to the left of the eighth dorsal vertebral spine and the second electrode was then placed in turn at each of the standard electrocardiograph positions V_{3R} and V_1 to V_6. A final tracing was made with one electrode in the V_6 position and the other in the V_{3R} (Fig 1) Fabric pads moistened with salt water were used between the electrodes and the skin (Burdick electropads) for speed and convenience. In all cases a separate light weight fine wire was attached with an alligator clip to each of the two electrodes and the other end of each wire was attached to the impedance converter Tracings were made with the subject in the supine position during held expiration to exclude respiratory artifacts. Repeat tracings were made on some normal individuals on successive days and months, and no differences were observed between the earlier and later tracings. The chest

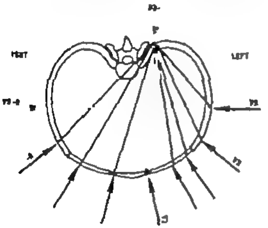


Fig 1 Positions of electrodes on skin of thorax. Straight lines indicate diameters measured between pair of electrodes.

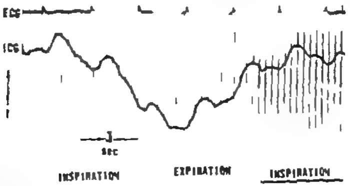


Fig 2 Impedance changes through right upper chest during respiration Arrow indicates direction of decreasing impedance (I). Impedance decreases during expiration as chest contract decreasing dist nce bet een electrodes.

electrodes must be applied with the same accuracy required for making routine electrocardiograms (ECG's).

The tracings presented here were chosen to demonstrate how changes in heart shape, chest size, and intrathoracic blood were represented in the impedance cardiogram (ICG). They were selected from the ICG's of 82 patients with heart disease proved by cardiac catheterization and 18 control subjects with normal hearts.

Observations on factors that change impedance of the thorax

INFLUENCE OF CHANGES IN CHEST SIZE AND PULMONARY BLOOD ON THE ICG. Fig. 2 shows the anterior posterior (AP) impedance tracings through the right upper chest of a patient with normal lungs. During inspiration the whole tracing shifts downward (increasing impedance) and during expiration the whole tracing shifts upward (decreasing impedance). The impedance varies directly as the distance between the electrodes which increases with inspiration. During each cardiac cycle the impedance decreased during systole and increased during diastole, inversely with pulmonary blood flow.

INFLUENCE OF NORMAL CARDIAC CHANGES ON THE ICG. The following test was done to see if impedance changes measured through the heart differed from impedance changes measured through the lung only. First, Fig. 3 compares impedance changes in the right lung with impedance changes in the left lung. Fig. 3 shows the vector oscilloscope display in which the right lung impedance is plotted as the abscissa against the left

Fig. 4. Vector oscilloscope display. Large loop made during systole indicates impedance changes measured through right upper chest differ from impedance changes measured through heart and lung in an AP diameter.

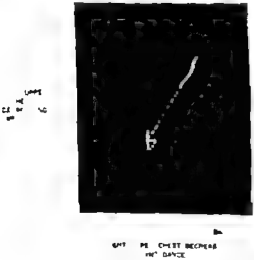


Fig. 3. Vector oscilloscope display. Straight line made during systole bisects the angle between ordinate and abscissa, indicating that identical impedance changes are being recorded from both right and left upper chest.

Fig. 5. Vector oscilloscope display. Large loop in systole and small loop in diastole indicate that impedance changes measured through heart and lung in an AP diameter differ from impedance changes measured in a right-to-left diameter through both heart and lung.

lung impedance as the ordinate. If any two identical signals are plotted in this manner the oscilloscope will display a straight line at 45° bisecting the angle between the ordinate and the abscissa. In this case, during systole there is such a straight line indicating that the impedance changes are identical in the two diameters measured. In diastole, a small loop is formed indicating that the impedance changes differ in the two diameters in this phase of the cardiac cycle. To compare impedance changes in the lung with those in the heart Fig. 4 shows the impedance through the right upper lung recorded as the abscissa and the impedance across the AP diameter

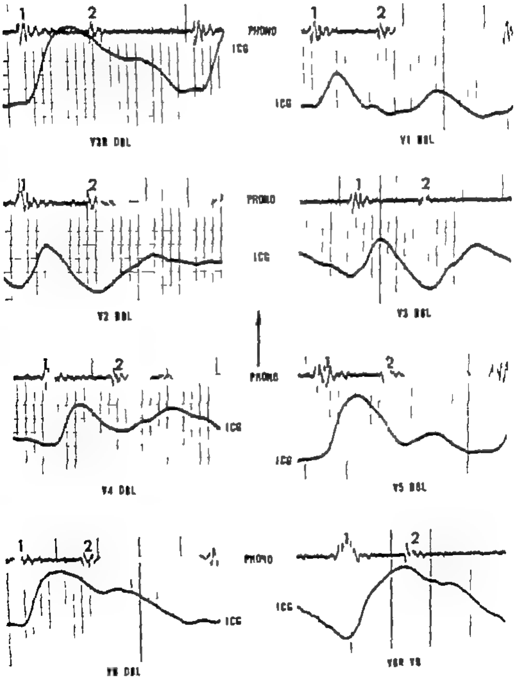


Fig. 6. Scalar ICG tracings from normal man in third decade of life. Arrow indicates upward movement of tracing is in direction of decreasing impedance. Positions of electrode pairs are indicated under each tracing.

of the heart and lung recorded as the ordinate. In systole a loop is formed indicating that the impedance changes through the heart differ from those through the lung In diastole another smaller loop reflects the same thing

Impedance changes through all diameters of the heart are not the same. Fig 5 shows the AP impedance changes through the heart and lung recorded as the ordinate and the right to-left, V_4 to V_{6R}, impedance changes recorded as the abscissa. The large loop during systole and the smaller loop during diastole indicate that the impedance changes through the heart differ in the two diameters. At the bottom of the figure the AP impedance changes are recorded as a scalar proceeding from left to right and at the left margin of the figure the right-to-left impedance changes are recorded as a scalar reading from down to up. Figs. 3 and 5 were all done on a normal woman in the fifth decade of life. Further evidence of asymmetrical impedance changes is shown in Fig 6 which are scalar tracings from a normal man in the third decade of life. The tracings from the rest of the 18 normal men and women were similar Three of the normal subjects differed from the others They showed an increase in impedance during systole in the diameters from D8L to V_{3R}, V_1 V_2, and V_3 instead of the usual decrease. Impedance tracings from different diameters of the same normal heart differed slightly showing asymmetrical impedance changes.

INFLUENCE OF ABNORMAL CHANGES IN HEART SHAPE AND MOTION ON THE ICG. Atrial flutter showed itself in the ICG s made through the atria plus the main mass of the left ventricle. Fig 7 presents an ICG made with one electrode at the left of the eighth dorsal spine (D8L) and the other electrode at the V_1 position. For each flutter wave in the ECG there is a corresponding undulation in the ICG indicating that the abnormal motions of the atria are represented in the ICG In another patient a small paradoxical bulge of the ventricle following a myocardial infarction produced localized ICG changes indicating increased impedance and increased diameter during systole. Fig 8 presents scalar tracings through the paradoxical bulge In the V_1 to D8L diameter instead of the normal upward movement of the tracing during systole (decreasing impedance) this tracing presents mostly a downward movement (increasing impedance) Fig 9 shows the aneurysm filled with contrast medium The increase in impedance during systole was related to

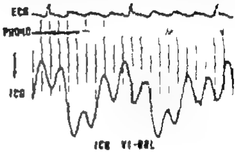


Fig 7 Scalar ICG in atrial flutter Arrow indicates downward movement of tracing is in direction of decreasing impedance. Position of electrode pairs indicated under tracing Each flutter wave ECG is accompanied by an undulation in ICG

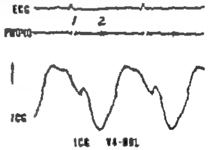


Fig 8 Scalar ICG measured through small ventricular aneurysm. Impedance increases when aneurysm bulges Arrow indicates upward displacement of tracing is in direction of decreasing impedance. Position of electrode pairs indicated under tracing

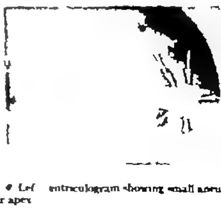


Fig 9 Left ventriculogram showing small aneurysm near apex

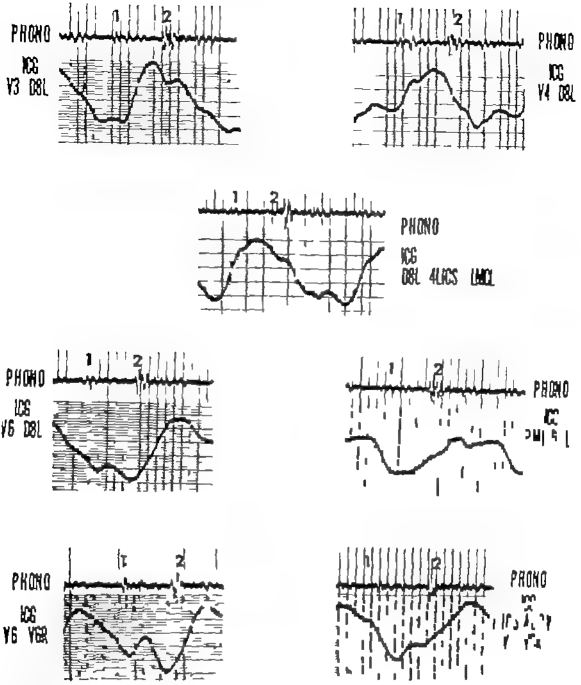


Fig. 10A. ICG tracings from a patient with aortic insufficiency, subacute bacterial endocarditis and severe congestive heart failure. Base of heart is contracting during systole and apex is simultaneously dilating. In each of the seven plates of this figure the phonocardiogram (*phono*) is the top tracing and the *ICG* is the bottom tracing.

Upward deflection of ICG indicates decreasing impedance and decreasing diameter of the base of the heart while it is contracting in systole. This is recorded between posterior electrode *D8L* and anterior electrodes V_3, V_4, and *4 LICS LMCL* (the top three plates in the figure).

Downward deflection of ICG indicates increasing impedance and increasing diameter of the apex of the heart during systole. This systolic dilation is recorded between the posterior electrode *D8L* and electrodes V_6 and *PMI* near the apex (these plates are in the middle of the figure).

Increasing right to-left impedance and diameter of the apex of the heart during systole is indicated by downward deflection of ICG recorded between electrodes V_6 and V_{6R}. Similar tracings were made with both electrodes one intercostal space higher (these plates are at the bottom of the figure).

Positions of electrode pairs are indicated beside ICG tracings. Notations V_3, V_4, V_6 and V_{6R} indicate standard electrocardiographic electrode sites where ICG electrodes were placed for these tracings. *D8L*, electrode to the left of the eighth dorsal spine. *PMI*, electrode at the point of the maximum left ventricular impulse. *4 LICS LMCL*, electrode at the fourth left intercostal space, left midclavicular line. *1*, first heart sound. *2*, second heart sound. Phonocardiogram recorded to indicate beginning and end of systole and diastole.

the increased diameter caused by the bulging of the left ventricular wall. Fig. 10A presents tracings from another patient with a paradoxical systolic bulge of the apex. This patient had aortic insufficiency, subacute bacterial endocarditis, and heart failure. His point of maximum left ventricular impulse (PMI) was forceful and displaced to the left and down. During systole while his PMI at the apex was bulging outward, the chest wall retracted over the base of the heart in the fifth left intercostal space 2 cm. to the left of the sternal edge and in the fourth left intercostal space in the left

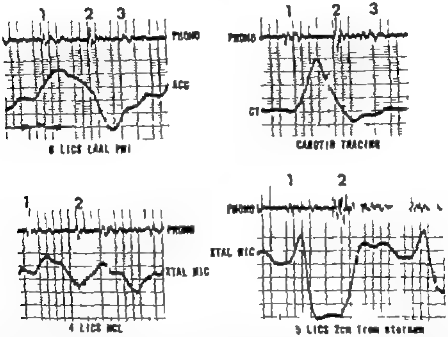
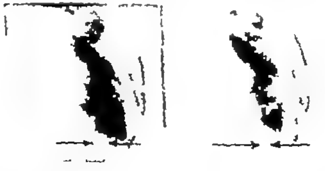


Fig. 10B. Physical movements of the chest wall from the same case of aortic insufficiency, subacute bacterial endocarditis, and severe congestive heart failure. Downward displacement shows retraction of the contracting base. Upward displacement shows the bulge of the dilating apex. *1*, First heart sound; *2*, second heart sound; *3*, third heart sound; lower tracing in each pair made with crystal microphone (*XTAL MIC*). *ACG*, apex cardiogram; *CT*, carotid tracing; *4 LICS MCL*, fourth left intercostal space midclavicular line, where movements of the chest wall were recorded with crystal microphone; *5 LICS*, fifth left intercostal space where movements of the chest wall were recorded with crystal microphone.

A



B

Fig. 11. *A*, Cinefluorogram of the same case of aortic insufficiency, subacute bacterial endocarditis, and congestive heart failure in end-diastole. Arrows show the distance between the rib edge and the cardiac border. *B*, Cinefluorograms of the same case in end-systole showing that the base of the heart contracted, but the apex expanded to the left. Both pictures made during the same held midinspiration. Arrows show less distance between the rib edge and the cardiac border.

midclavicular line. The top three tracings of Fig. 10*A* show decreasing impedance at the base of the heart during systole; the bottom four tracings show increasing impedance at the apex. Fig. 10*B* presents the physical movements of the chest wall recorded with a low frequency Sanborn crystal microphone. Outward *movement* caused an upward deflection of the tracing. Fig. 11,*A* shows a frame in diastole and Fig. 11,*B* a frame in systole from a cinefluorogram of this patient's heart recorded in the supine position. In systole the base of the heart contracted but the apex ex-

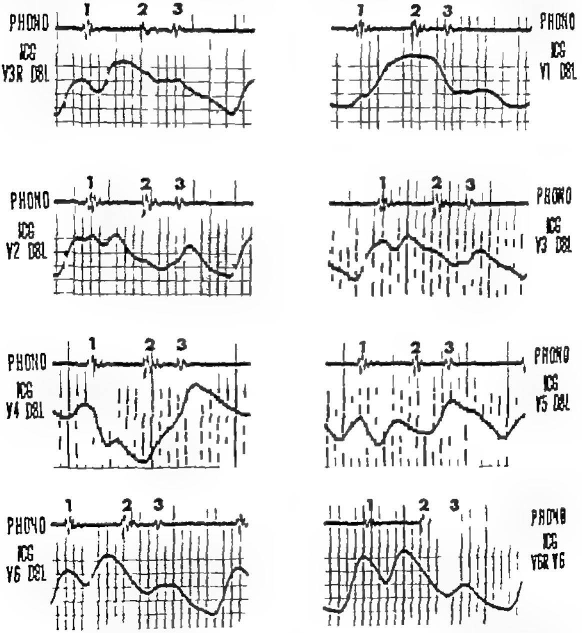


Fig. 12*A*. Scalar ICG tracings in restrictive myocardial disease. In each of the eight plates in this figure the upper tracing is the phonocardiogram (*phono*) and the lower tracing is the *ICG*. The upward movement of the ICG after the *third heart sound* in diastole indicates decreasing impedance which occurred during extremely rapid symmetrical filling of the left ventricle. This presented an increasing cross-sectional area (which decreased impedance) to most diameters and it concealed the lesser simultaneous increase in impedance due to increasing diameters. *1*, First heart sound; *2*, second heart sound; *3*, third heart sound. Sites of electrodes are indicated beside each ICG tracing.

panded This was also observed in other cases of heart failure

Symmetrical ventricular filling decreased impedance. Fig 12*A* presents scalar impedance tracings from a 21 year-old man with restrictive myocardial disease. In diastole this heart dilated very rapidly and stopped dilating so suddenly that it shook the whole mediastinum Naturally this produced a third heart sound This fairly symmetrical dilation decreased impedance in all leads excepting one (Fig 12*A*) The impedance tracing after reaching the peak of decreased impedance dropped back gradually to the point of origin in all tracings This was partly due to the time constant of the impedance converter which made the tracings return two thirds of the way to the point of origin in 0.5 second (Fig 12*B*) Obviously all the other movements of the impedance tracing were too rapid to be the result of the time constant. During systole the left ventricle especially the apical region emptied poorly as can be seen in Fig 13 *A* and *B* The tracings in systole show decreasing impedance in some diameters but increasing impedance in V_4 and V_6, which were measured through the apex of the heart. Thus, changes in the heart shape made impedance change in the following manner (1) Generalized dilation of the heart decreased impedance in most leads because the cross-sectional area presented to most leads increased (2) Disproportionate decreases in diameter decreased impedance and failure of a diameter to decrease proportionately increased impedance. (3) Disproportionate increases in diameter increased impedance.

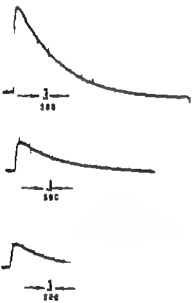


Fig 12B Time constant tracings showing that the tracing returns to the baseline in the same length of time regardless of the amount of displacement if no further change in signal occurs after the initial impedance change

In some heart diseases well known phasic heart motions can be detected by the ICG along certain diameters only These phasic motions are commonly recorded by the apexcardiogram (ACG) Fig 14 from a patient with atrial septal defect shows simultaneous recordings of an ACG and an ICG that resembled the ACG This ICG could only be recorded along the diameter from D8I to the sixth intercostal space at the midclavicular line. Fig 15,*A* presents a simultaneous ACG and ICG from a patient

Fig 13 A Left ventriculogram in the same case of restrictive myocardial disease at the end of diastole *B* The same case of restrictive myocardial disease at the end of systole showing poor emptying

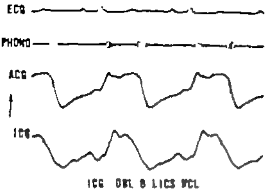


Fig 14 Simultaneous ACG and ICG from a patient with atrial septal defect showing similarity of contours. Location of electrode pairs for ICG indicated under the tracing. *D8L*, left of the eighth dorsal spine; *6 LICS MCL*, sixth left intercostal space, midclavicular line.

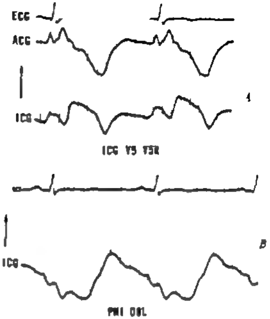


Fig 15 *A*, Simultaneous ACG and ICG in idiopathic hypertrophic subaortic stenosis showing similarity of contours. Positions of electrode pairs for ICG indicated under tracing. Arrow indicates direction of decreasing impedance. The ICG shows decreasing impedance and decreasing right-to-left diameter throughout systole. *B*, ICG from the same case of the idiopathic hypertrophic subaortic stenosis with posterior electrode at the left of the eighth dorsal spine and anterior electrode at the point of the maximum impulse which was the fourth left intercostal space, left midclavicular line. Increasing impedance in systole indicates anterior-posterior diameter is not decreasing as much as right-to-left diameter.

with idiopathic hypertrophic subaortic stenosis. This ICG too resembles the ACG and it could only be recorded along the right-to-left diameter V_{5R} to V_5. This tracing shows decreasing impedance and decreasing right-to-left diameter throughout systole.

Discussion

The evidence presented in this report shows that ICGs truly reflect cardiac activity. It has been claimed that ICGs result from changing pressures at the electrode-electrolyte interface, that is, changing pressure of the skin against the electrode.[7] Increase in such pressure improves the contact and decreases impedance. If this influenced ICGs significantly, then during systole when the point of maximum impulse presses against the electrode placed over it, we should record a decreasing impedance. However, in the tracings from the overactive point of maximum impulse in the case of idiopathic hypertrophic subaortic stenosis impedance actually increased rather than decreased during systole (Fig 15,*B*). Impedance change resulting from the change in the shape of the heart was greater than any variation which might have occurred at the electrode-electrolyte interface.

Impedance changes reflect the condition of the heart. In the best condition maximum useful cardiac work occurs when there is maximum muscle tension in the isovolumetric period and maximum shortening during ejection.[8] This happens in the normal left ventricle. It begins with asynchronous contraction in the isovolumetric period. Internal diameter, external circumference, and length increase as the papillary muscles pull the mitral valve into the ventricular cavity.[9] These changes in the heart shape are recorded in the ICG tracings presented here. Variations from this pattern decrease effective heart work and they appear in ICGs as abnormal deflections.

During ejection in heart disease the ICG shows what parts of the heart are *failing*. In a heart where some fibers are *infarcted*, others ischemic, and others healthy, the myocardium does not fail symmetrically. The same differences in myocardial contraction occur in the *enlarged* heart which has some areas that protrude and others

that shorten during systole.[10] This interferes with blood ejection. Normally the tensed muscles hurl blood out of the ventricular cavity like a stone out of a sling shot. Most of the energy is delivered in early systole giving great momentum to the blood mass as it moves along the outflow tract. Muscle tension and cavity pressure decrease as the muscle shortens rapidly during ejection. In the latter half of systole blood flows by momentum from the lower pressure ventricle to the higher pressure aorta.[11] In heart disease, the contraction of healthy muscle fibers stretches injured fibers, wasting work and making ventricular dyssynergy. The electrical ICG's presented in this study located these regions of myocardial dysfunction.

Summary

1. The electrical impedance cardiogram (ICG) records continuous changes in heart shape throughout the cardiac cycle. It can be recorded on any direct writing electrocardiograph.

2. Certain electrical impedance cardiograms closely resembled mechanical displacement recordings of heart motion (apex cardiograms) indicating a related origin.

3. Tracings from normal subjects resembled each other but tracings from patients with known cardiac deformities differed from the normal.

4. Atrial activity was recorded selectively.

5. Paradoxical bulges of the left ventricle produced characteristic abnormalities in impedance cardiograms.

6. The impedance cardiogram can be used to analyze dynamic dysfunctions of the heart.

The authors express their appreciation to Mr. John Hall for his technical work in making some of the tracings.

REFERENCES

1. Rushmer R. F., Crystal, D K., Wagner C. and Ellis, R M. Intracardiac impedance plethysmography. Am. J. Physiol. 174:171, 1953.
2. Geddes, L. A., Hoff H. E., Mello, A., and Palmer C. Continuous measurement of ventricular stroke volume by electrical impedance, Baylor University Cardiovascular Research Center Bulletin 4:(4), 118, 1966.
3. Klinnen, E. Kubicek, W. and Witsoe, D. Thoracic cage impedance measurements, USAF School of Aerospace Medicine, Technical Documentary Report No. SAM TDR-64-23, May 1964.
4. Kubicek, W. G., Karnegis, J. N., Patterson, R. P., Witsoe, D. A., and Mattson, R. H. Development and evaluation of an impedance cardiac output system, Aerospace Medicine 37:1208, 1966.
5. Nyboer J. Electrical impedance plethysmography, Springfield, Ill. 1959 Charles C Thomas Publisher.
6. Hawthorne E. W. Instantaneous dimensional changes of the left ventricle in dogs, Circulation Res. 9:110, 1961.
7. Hill, R. B., Jansen, J. D. and Fling J. L. Electrical impedance plethysmography: A critical analysis, J. Appl. Physiol. 22:161, 1967.
8. Linzbach, A. J. Heart failure from the point of view of quantitative anatomy. Am. J. Cardiol. 5:370, 1960.
9. Rushmer R. G. Initial phase of ventricular systole. Asynchronous contraction, Am. J. Physiol. 184:188, 1956.
10. Langley J. O., Martinez, A., Fakhro, A., Durokan P. and Harrison, T. R. Paradoxical precordial motion and wasted left ventricular work. The concept of cardiac dyssynergy. Am. Heart J. 73:349, 1967.
11. Spencer M. P. and Greiss, F. C. Dynamics of ventricular ejection, Circulation Res. 10:274, 1962.

Case reports

Reflex bradycardia and nodal escape rhythm in pheochromocytoma

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Palpitations are often a prominent symptom in patients with pheochromocytoma and paroxysmal attacks of hypertension.[1-4] Premature contractions or tachycardia of atrial or ventricular origin are frequent during the hypertensive crisis. The ectopic beats are presumably secondary to stimulation of cardiac pacemakers by elevated blood catecholamine concentrations. However, depression of the sinus pacemaker with escape of lower pacemakers elicited by rapid rise of blood pressure to very high levels has been infrequently described.

We are reporting two patients who developed intermittent chest pain with arrhythmia. Both were admitted to a coronary care unit because of a suspected diagnosis of acute myocardial infarction. Both proved to have pheochromocytoma with paroxysmal episodes of hypertension. Constant monitoring of the electrocardiogram (ECG) revealed that sinus slowing with atrioventricular dissociation and palpitations developed coincident with the hypertension.

Case reports

Case 1. F. W., a 69-year-old Caucasian man, noted the onset of nausea, *substernal aching pain,* and forceful thumping in his chest while visiting his wife, a patient in the hospital. Examination revealed a regular pulse of 140 beats per minute and blood pressure of 130/80 mm. Hg. An ECG taken during recurrence of symptoms showed sinus bradycardia with atrioventricular dissociation and slow "nodal" (junctional) rhythm. A tentative diagnosis of acute myocardial infarction *prompted immediate* admission to the coronary care unit.

Six months previously, his physician had prescribed antihypertensive medication for elevated blood pressure. Later, the blood pressure was normal and medication was discontinued. Intermittent episodes of forceful thumping in the chest associated with substernal pressure developed four months prior to admission. These attacks *recurred repeatedly* and were often associated with lightheadedness, and on one occasion with syncope.

Physical examination on admission revealed *regular pulse of 110 beats per minute.* Blood pressure was 140/80 mm. Hg. The rectal temperature was 38° C. and respirations were 14 per minute. The skin was smooth, dry, and pale. The pupils were normal in size and reacted, and examination of ocular fundi showed minimal arteriolar narrowing. The chest was clear. The heart was normal in size. A soft systolic murmur was heard at the apex. No masses or organs were palpated in the abdomen.

Urinalysis was normal. The hematocrit was 49 per cent. A white blood cell count was 12,000 per cubic millimeter. The differential was normal. Blood urea nitrogen was normal.

Constant monitoring of the ECG revealed episodic sequences of arrhythmia (Fig. 1). Sinus bradycardia gradually developed and was followed by nodal escape with atrioventricular dissociation. Nor-

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mal AV conduction returned and the sinus rate increased. Serial indirect blood pressure measurements revealed gradual rise from 120/80 to 250/100 mm. Hg during the development of the arrhythmia followed by fall to 80/60 mm. Hg. Symptoms recurred during many of the hypertensive episodes.

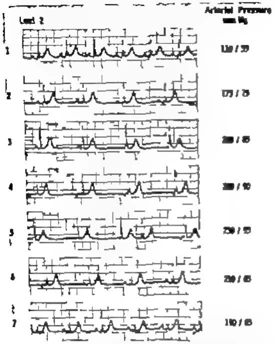

Fig. 1. Sequential changes in cardiac rhythm during an episode of hypertension in Case 1 demonstrating slowing of the sinus pacemaker and nodal escape rhythm with A-V dissociation as the blood pressure rises, and restoration of sinus rhythm culminating in sinus tachycardia, as the blood pressure falls toward normal (paper speed 25 mm. per second).

A arterial catheter was inserted in the patient brachial artery by percutaneous Seldinger technique, and blood pressure and ECG recorded simultaneously. The relationship of the blood pressure changes to the arrhythmia is illustrated i Figs. 1 and 2. A rise in blood pressure always preceded the onset of arrhythmia. Sinus rhythm returned as arterial pressure fell toward normal. A complete cycle of hypertension and arrhythmia required 7 to 10 minutes. Attacks varied in frequency and were only occasionally correlated with emotional stimuli.

Plasma volume, calculated following intravenous injection of radioactive iodinated serum albumin, was 37 ml. per kilogram (normal 45± 10 ml. per kilogram). Estimated whole blood volume was 63 ml. per kilogram (normal 70± 15 ml. per kilogram).

Cardiac index, determined by the indicator dilution technique following intravenous injection of indocyanine green, was 1.80 L. per minute per square meter. Arterial pressure was 115/39 mm. Hg and calculated peripheral vascular resistance was 2,000 dynes per second per centimeter^{-5}. The patient did not have spontaneous hypertension during these measurements and no attempt was made to induce an attack.

Blood catecholamine levels are shown in Table I. Chemical studies of urine were as follows: (1) catecholamines in µg for 24 hours: preoperatively 424, postoperatively 126, normal <250; (2) metanephrine and normetanephrine in µg per 0.2 mg. of creatinine: preoperatively 0.75, postoperatively <0.15, normal <0.15; (3) 3-methoxy-4-hydroxyphenyl glycol in µg per 0.2 mg. of creatinine: preoperatively 0.50, postoperatively <0.15, normal <0.15.

Several days later the patient underwent laparotomy. During induction of anesthesia, blood pressure rose to 262/105 mm. Hg, and the arrhythmia reappeared. Massage of the right adrenal gland produced a similar response. After well-encapsulated 40 Gm. pheochromocytoma was excised from the right adrenal, blood pressure fell to 70/50 mm. Hg.

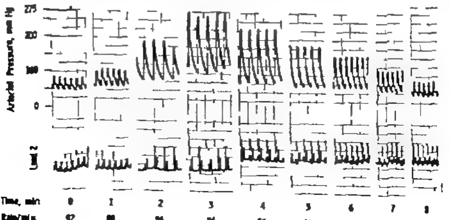

Fig. 2. Simultaneous ECG and direct arterial pressure during another paroxysm of hypertension in Case 1. Note relationship between change in blood pressure and development of the arrhythmia (paper speed 5 mm. per second).

Table I. Plasma levels of epinephrine and norepinephrine in two cases of pheochromocytoma with reflex bradycardia and nodal escape rhythm

	Blood pressure (mm. Hg)	*Plasma epinephrine (μg/L. plasma)*	*Plasma norepinephrine (μg/L. plasma)*
Normal range		<2 0	<6 6
Case 1			
Control	154/80	1 3†	3 8†
During hypertensive attack			
Onset	80/50	2 6	3 5
Rising	205/68	26 7	3 6
Peak	240/130		
Falling	198/73	2 9	3 4
Case 2			
Control	158/80	3 1†	8 2†
During hypertensive attack			
Peak	300/160	28 5†	27 3†

Kindly performed by Dr. William Manger Columbia-Presbyterian Medical Center New York City.
†Average of two rapid sequence samples.

Intravenous administration of norepinephrine produced transient rise in blood pressure to 200/100 mm. Hg, and again sinus bradycardia with nodal escape and atrioventricular dissociation occurred. By the end of the operative procedure the patient heart rate, rhythm, and blood pressure were normal and further medication was not required. Postoperatively the patient did well. He has remained normotensive.

Case 2. W. W. 58-year-old Caucasian man was admitted to a coronary care unit because of attacks of chest pain and palpitations. He described episodes of slow strong pounding in the chest associated with abdominal cramps, sweating pallor anterior chest pain and pressure in the head.

Symptoms had begun five years previously shortly after he underwent a vagotomy for marginal ulcer. A subtotal gastrectomy had been performed ten years earlier for peptic ulceration with bleeding. Mild diabetes mellitus was diagnosed four years prior to admission. Two years prior to admission, pheochromocytoma was suspected after a transitory episode of hypertension, but diagnostic tests were all within normal limits. In the week prior to admission the patient symptoms increased markedly.

Physical examination revealed a healthy man in no apparent distress. Heart rate was 62 beats per minute. The blood pressure was 160/70 mm. Hg. Multiple soft, mobile nontender subcutaneous nodules were present on the arms, back, and abdomen. The pupils and ocular fundi were normal. The chest was clear to percussion and auscultation. The heart was slightly enlarged with moderate apical beat suggesting left ventricular enlargement. A soft, short, nonradiating systolic murmur was heard along the upper left sternal border. No organs or masses were palpated in the abdomen.

There was moderate glucosuria. Complete blood count and blood urea nitrogen were normal. Fasting blood glucose was 214 mg. per 100 ml.

The patient was monitored for several days in coronary care unit. Episodes of hypertension and arrhythmia coincided. As the blood pressure rose from 140/80 mm. Hg to as high as 300/190 mm. Hg, sinus bradycardia developed, followed by nodal rhythm and AV dissociation (Fig. 3). The patient would complain of pressure and pounding in the chest with abdominal cramps. His face would become ashen and occasionally diaphoretic. After 3 to 6 minutes, as the blood pressure fell, his symptoms would improve and the rhythm would revert to sinus tachycardia. Occasional atrial or ventricular premature complexes occurred during a hypertensive cycle. The attacks occurred spontaneously and could be induced by massage of either the right or left abdomen.

Urinary catecholamines were within normal limits. Urinary vanillomandelic acid was 10.8 mg. for 24 hours (normal 0 to 10 mg. for 24 hours). Plasma epinephrine and norepinephrine levels obtained during an induced attack were markedly elevated (Table I). Nephrotomograms and presacral gas insufflation showed enlargement of the superior pole of the right kidney. Renal arteriography was normal.

Histologic sections of subcutaneous nodule revealed angiolipoma.

A diagnosis of pheochromocytoma was considered established but the patient refused an exploratory operation and was treated with phentolamine 50 mg. by mouth every four hours with alleviation of symptoms.

Discussion

Although about 75 per cent of patients with pheochromocytoma complain of palpitations their symptoms usually reflect tachycardia. The palpitations are often overshadowed by other sympathetic manifestations such as sweating anxiety pallor

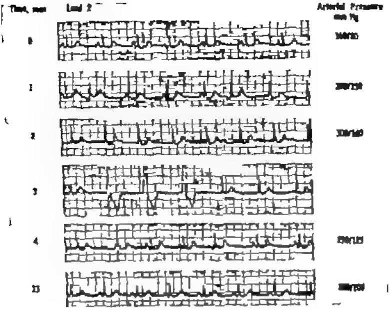

Fig. 3. Sequential changes in cardiac rhythm during an episode of hypertension precipitated by massage of right upper abdominal quadrant in Case 2. Note depression of sinus pacemaker and appearance of lower foci as blood pressure rises. When blood pressure declines, sinus mechanism is restored (paper speed 25 mm. per second).

headache, nausea, vomiting, and tremor. The symptoms of both our patients were primarily thumping in the chest and precordial pain. Aside from intermittent hypertension they exhibited few other symptoms or signs of paroxysmal catecholamine release. Indeed the diagnosis might well have been overlooked in both patients if they had not been admitted to a coronary care unit with a tentative diagnosis of acute myocardial infarction. With continuous monitoring of the ECG the correlation between arrhythmia and intermittent hypertension was recognized. Observation of the sequence of blood pressure rise and arrhythmia permitted correlation of these changes with the marked increases in the blood level of circulating catecholamines (Table I).

A rise in arterial pressure stimulates the baroceptors and evokes reflex vagal discharge which slows the sinus pacemaker. In the two patients presented herein the relationship of the rise in arterial pressure to the slowing of the sinus rate was clearly demonstrated. When the hypertension was most severe, nodal escape and atrioventricular dissociation occurred. Notable was the lack of ventricular escape or enhanced ventricular automaticity. Although some ectopic atrial activity occurred, the dominant arrhythmia in both patients was escape of lower pacemakers secondary to suppression of the normal mechanism during the episodes of hypertension. Arrhythmia developed during the phase of rising pressure. Sinus rhythm returned during the falling phase when pressure was considerably above the resting level.

The occurrence of sinus depression and AV dissociation without ectopic ventricular beats in association with the paroxysmal hypertension of pheochromocytoma has been documented twice previously. Burgess and associates[5] reported the case of a 23-year-old woman with pheochromocytoma who had episodes of sinus bradycardia with frequent nodal escape beats, often in a bigeminal rhythm with retrograde atrioventricular block, associated with her hypertensive crises. Espersen and Jorgensen reported the case of a 49-year-old man with pheochromocytoma who also developed sinus bradycardia, nodal escape rhythm, and intermittent sinus capture during paroxysmal hypertensive attacks. This patient had episodes

of atrial premature contractions and atrial fibrillation.

The rarity of reports describing arrhythmias due to depression of primary pacemakers in pheochromocytoma is surprising since the normal vagal response to an elevation of blood pressure is sinus slowing. Sinus tachycardia, premature beats, and ectopic tachycardias are the arrhythmias most commonly recorded in patients with pheochromocytoma, suggesting that the stimulating effect of the circulating catecholamines overrides or masks the reflex vagal response in most cases. Our recognition of two instances of arrhythmia due to depression of normal pacemaker in less than six months suggests that this phenomenon may be more common than generally assumed.

Summary

Two patients are described in whom the presenting symptoms of pheochromocytoma were related to reflex sinus bradycardia and nodal escape rhythm. The mechanism underlying this arrhythmia is illustrated and discussed. Although rarely reported previously, the diagnosis of pheochromocytoma should be considered in patients with intermittent bradycardia and escape of lower pacemakers. If in this circumstance serial measurement of blood pressure reveals episodic hypertension during the arrhythmia, specific tests may establish a diagnosis of pheochromocytoma.

REFERENCES

1. Gifford, R. W., Kvale, W. F., Maher, F. T., Roth, G. M., and Priestley, J. T.: Clinical features, diagnosis and treatment of pheochromocytoma: A review of 76 cases, M yo Clin. Proc. 39:281, 1964.
2. Watkins, D. B.: Pheochromocytoma. A review of the literature, J. Chron. Dis. 6:510, 1957.
3. Cahill, G. F.: Pheochromocytoma, B ll. New York Acad. Med. 29:749, 1953.
4. Durant, J., and Soloff, L. A.: Arrhythmic crisis of pheochromocytoma, Lancet 2:124, 1962.
5. Burgess, A. M., Waterman, G. W., and Cutts, F. B.: Adrenal sympathetic syndrome and unusual variations in cardiac rhythm, Arch. Int. Med. 58:433, 1936.
6. Espersen, T., and Jørgensen, J.: Electrocardiographic changes in paroxysmal hypertension due to chromaffin adrenal tumor, Acta med. scandinav. 127:494, 1947.
7. M oyer, William M., editor: Hormones and hypertension, Springfield, Ill., 1966, Charles C Thomas, Publisher.

Hyperkalemic intermittent paralysis associated with spironolactone in a patient with cardiac cirrhosis

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Disturbances of potassium metabolism represent serious problems in the diuretic treatment of cardiac, hepatic, and renal edema. Following the introduction of sulfonamide diuretics and corticosteroids, attention was focused mainly upon the hazards of hypokalemia.[1-4] However, since compounds inhibiting renal tubular potassium secretion (e.g., spironolactone and triamterene) have been used, complications associated with hyperkalemia must also be given earnest attention. Recently, fatal flaccid muscular paralysis has been observed in a patient with refractory edema treated with spironolactone,[5] similar to the hyperkalemic paralysis in renal failure[6-21] or Addison's disease.[22] In the case of cardiac cirrhosis described here, flaccid paraplegia developed during spironolactone (Aldactone-A) treatment and was treated successfully with aldosterone (Aldocorten), furosemide (Lasix), and acetazolamide (Diamox).

Report of case

A 42-year-old woman was admitted on July 6, 1966. At the age of 8 years, she had had arthritis and carditis. She was in the hospital for the first time at the age of 39 because of heart failure. At the time of the present admission, she was absolutely refractory to the combination of mercurial diuretic and chlorothiazide.

She was very thin and pale, with generalized muscle wasting. There was enormous ascites. The percussion sound over the lungs was hypersonorous. A few fine râles could be heard over both bases. The heart was enlarged by two fingers' breadth to the right of the sternum; to the left it extended to the midaxillary line. At the apex, loud holosystolic murmur, a decrescendo diastolic murmur, and an opening snap could be heard. Over the pulmonary area a decrescendo diastolic murmur was detected, different from that at the apex. The pulse rate was 72 per minute, easily suppressible; the blood pressure was 120/75 mm. Hg. After the ascites had been drained, an enlarged liver and spleen could be palpated.

Laboratory findings. Urinalysis showed the urobilinogen to be increased, but was otherwise negative. The red cell count was 3.1 million per cubic millimeter; the hemoglobin was 10.5 Gm. per 100 ml.; the white cell count was 4,000 per cubic millimeter, with a differential count of stab cells 8 per cent, polymorphonuclear leukocytes 60 per cent, eosinophils 3 per cent, monocytes 11 per cent, and lymphocytes 18 per cent. The nonprotein nitrogen (NPN) was 34 mg. per 100 ml.; the serum bilirubin was 2.0 mg. per 100 ml. Result of the thymol test was 5.6 units; of the gold sol test, 2 units. The serum glutamic oxalacetic transaminase (SGOT) was 120 units; the blood sugar was 93 mg. per 100 ml.; the creatinine clearance was 63 ml. per minute; the serum creatinine was 0.87 mg. per

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100 ml. The serum sodium was 140 mEq. per liter potassium 4.5 mEq. per liter chloride 85 mEq. per liter bicarbonate, 25 mEq. per liter. The serum sodium and potassium values during the 278 days of treatment are shown in Figs. 1 to 3. Serum chloride ranged from 87 to 108 mEq. per liter. The NPN content remained below 35 mg. per 100 ml. throughout. Radiography of the chest revealed transparent lung fields cor bovinum, an enormously enlarged pulmonary arc, dilated blood vessels in the hilum, pericardial adhesions, and a narrowed retrocardium. In the electrocardiogram (ECG), R deviated to the right, and there was extreme disturbance of repolarization.

Clinical course. Because of refractory ascites, spironolactone administration was begun on the day of admission with daily doses of 200 mg. The combined diuretic treatment was highly effective (Fig. 1).

In view of the increase of the serum potassium level to 5.8 mEq. per liter spironolactone was discontinued (period I). Immediately the effect of diuretics diminished and edema increased. Spironolactone was then reintroduced (period II) the diuretics became effective again. From the day 79 on prednisolone was also given (Figs. 1 and 2).

Between the days 146 and 155 weakness developed, while the serum potassium concentration was 6.1 mEq. per liter and increased to 6.8 mEq. per liter. The facial expression of the patient changed characteristic lid lag developed,[18] and she became somnolent. Experience had shown us many times that this too was a clinical manifestation of potassium intoxication we thought it to be so characteristic that subsequently we could diagnose the electrolyte disturbance by simply looking at the patient. We did not discontinue spironolactone completely but only reduced the dose. Edema formation started right away. The serum potassium level did not decrease but the symptoms of potassium intoxication subsided completely.

With the administration of diuretics between days 163 and 168, the hyperkalemic effects of the increased dose of spironolactone could be prevented temporarily. Also the edema was eliminated. On day 183 pronounced weakness developed once more although the serum potassium concentration was not more than 5.7 mEq. per liter. Spironolactone was discontinued and the weakness improved within four days, although the serum potassium concentration decreased only to 5.2 mEq. per liter. Edema and ascites recurred.

Insulin treatment between days 177 and 204 failed to influence demonstrably the hyperkalemia. Edema increased and spironolactone treatment was therefore resumed on day 188. Weakness severe enough to cause extreme difficulty in walking developed for the first time on day 222 not exactly parallel, but about the same time the serum potassium concentration reached the peak 8.7 mEq. per liter. The patient had to stop walking after a

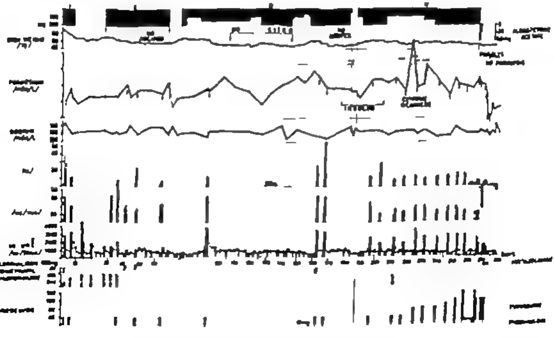

Fig. 1. Important clinical and laboratory data during the 279 days of hospital treatment. When spironolactone administration was started four times the serum potassium level increased lowering the dose followed by a decrease of serum K level. Potassium intoxication developed for the first time in period III (+ = somnolence ++ = muscle weakness +++ = ECG changes). Aldosterone and furosemide or acetazolamide lowered hyperkalemia and abolished paralysis in period IV the glomerular filtration rate remarkably reduced. (The black columns represent data obtained on days of diuretic administration.)

few steps and had to lean against something until she could start walking again. The dose of spironolactone was immediately reduced to 100 mg., during the next 24 hours, weakness lessened somewhat, and 24 hours later disappeared almost completely.

Between days 261 and 264 the patient found it difficult to get out of bed, but she was able to walk. In spite of the high dose of furosemide combined with spironolactone, ascites and edema increased. On day 266 the patient told us that on day 265 she had been unable to get up from the toilet. When in bed, she could not elevate or pull up her legs, nor could she dorsiflex the feet. The tendon reflexes could not be elicited in the legs. Although the hands, too, were weak, she could move them well. Tendon reflexes in the arms were exaggerated. She was unable to raise her head from the pillow unless she helped herself by the hands and she was unable to sit up in bed. A few hours later she was helped up and could shuffle a few steps. When put back to bed, she was unable again to raise her head, sit up, or raise her legs. The changes in serum electrolyte concentrations are shown in Fig. 2. NPN was below 35 mg. per 100 ml.

For two days after administration of intravenous aldosterone and furosemide (days 267 and 268) she was much better: she could elevate and pull up her legs, raise her head, sit up unassisted, and walk with less difficulty (Fig. 2). Leg reflexes returned. After that, weakness developed again and the serum potassium level increased slightly. In response to diuretic administration she felt better again and could get up unassisted. Serum potassium was 4.0 mEq. per liter. She died of intercurrent pneumonia on day 279.

Abstract from the necropsy protocol. The cadaver was extremely thin, with excessive muscle wasting. The heart weighed 510 grams. The right ventricle was enormously dilated; the pulmonary cone was excessively dilated; the pulmonary cusps were thickened; the tricuspid valve was cicatrized, thick and rigid; the opening slitlike; the left ventricle was enormously dilated; three fingers could be inserted into the aortic bulb whereas from the descending part of the aortic arc downward only one finger could be inserted into the aorta; the aortic cusps were stiff, thickened, and deformed. The liver weighed 1,050 grams; on the cut surface, the total disintegration of the hepatic structure was striking. The kidneys were of average size, the surface finely granular.

Diagnosis. Rheumatic valvular heart disease

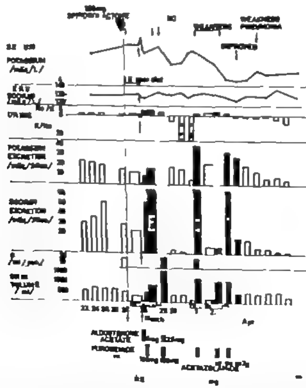

Fig. 2. Details of data for periods immediately preceding and following hyperkalemic paralysis. In the last spironolactone period there was oliguria, low glomerular filtration rate, low Na/K ratio, and hyperkalemia. As administered alone after the development of paralysis, aldosterone reduced water, sodium, and potassium excretion; therefore, the serum potassium concentration continued to increase for a time. On the administration of furosemide, however, potassium excretion was increased, hyperkalemia diminished, and paralysis disappeared. When the serum potassium level increased and weakness appeared again, a combination of furosemide and acetazolamide was administered with good results.

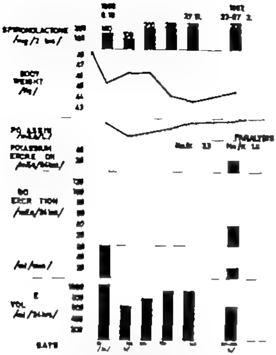

Fig 3 Relationship between dose and response t spironolactone. At the onset of treatment, th diuretic action of 150 t 200 mg of spironolactone a day (as judged by diuresis and loss of body eight) was much higher than that of the 100 mg dose In the last period, loss of potency was indicated by decreased urine nd sodium output Despite the decreased rinary Na/K ratio, the absolute potass m output alo decreased, although i tak was nchanged The decrease of GFR is conspicu-ous. (The figures brackets how the number of day from which mean lues were computed)

mitral stenosis nd insufficiency organic pulmonary nd ortic insufficiency f nctional tricuspid insuf ficiency arteriosclerosis aortae concretio peri cardii cardiac irrhosis of the liver bronchopneu-monia

Histologic study The kidneys showed marked arteriolosclerosis, with secondary glomerulosclerosis, nd there was most conspicuous hyperplasia of the j taglomerular pparatuses. The juxtaglomer ular granulation index was 8 4 per cent, moderately elevated I the adrenal cortex every zone was thinner Compact cells outnumbered l pid-bearing cells. At some sites few heaps of cells (hyper plastic nod les) th high lipid content were isible The muscle fibers aried extremely in thickness there were ollen fibers beside very thi fibers. In the swollen fibers, longitud nal striation w maintained, but was dis tegrated granularly t some sites Transverse triations ere almost tot lly bsent Sarcolemmal nuclei were I tact.

Discussion

In this case of cardiac cirrhosis with refractory ascites, hyperkalemic flaccid paralysis developed in the legs with only moderate weakness elsewhere Hyperkalemia could be reduced and apparently this prevented the paralysis from spreading proximally

The elevation of serum potassium level was undoubtedly due to spironolactone medication (Table I Figs. 1 to 3) Spironolactone alone was responsible for the hyperkalemia as there was no azotemia

Hyperkalemic paralysis has been observed until now in the presence of azotemic renal failure in patients with kidney disease [8,19] Addison s disease [11,21] and refractory edema treated with spironolactone or triameterene Hyperkalemic paralysis without azotemia was described only in the adrenalectomized case of Bell and associates[22] and familial hyperkalemic periodic paralysis.[24] In the hereditary condition paralysis is intermittent and transient varies from mild leg weakness to flaccid quadriplegia with weakness of the cervical muscles and is not necessarily accompanied by extreme hyperkalemia[2] In our case the intermittent weakness resembled the hereditary disease very closely There was no rigid correlation between the signs and symptoms of potassium intoxication and serum potassium (Fig 1)

Spironolactone causes hyperkalemia through its antialdosterone action ie by blocking the distal tubular sodium potassium exchange [4,25] Presumably spironolactone also has an extrarenal effect[3] This view is supported by our observation that in the period of spironolactone treatment without the simultaneous administration of diuretics (Section III of Fig 1) hyperkalemia existed when pot ssium intake and output were balanced (about 40 mEq intake and output)

During the most effective period of the so-called potassium retaining spironolactone treatment (Fig 1 Section III Fig 3 days 137 to 145) despite more intensive inhibition of dist il tubular pota ium secretion (higher N K ratio) twice the amount of pota ium w [illegible] nated in the urine than later (Fig 1 Section IV Fig 3 Days 261 to 265) This implies that for the el mination of more potas ium more sodium w s at the di posal of the distal ion exchange mechani m Although these changes might be lue to the

Table I

Periods (according to Fig. 1)	*Average dose of spironolactone (mg./24 hr.)*	*Average serum potassium concentration (mEq./L.)*	*No. of determinations*	*Paresis or intoxication*
Control	—	4.50	1	—
I–II	200	4.54	18	—
III	161	5.93	19	+
IV	161	6.17	29	+++
During discontinuation of therapy	—	5.23	8	—

inhibition of sodium reabsorption in proximal tubules by spironolactone, the role of the higher glomerular filtration rate could not be excluded.

Recent evidence indicates that aldosterone and its specific antagonist act also at the proximal tubular level.[28,29] This is supported by observations during treatment of the hyperkalemic paralysis of this patient. During the first two hours following aldosterone administration, sodium *and* potassium excretion diminished *together* and the serum potassium concentration, high anyway, increased even more (Fig. 2). It is obvious that, as a result of increased proximal reabsorption, insufficient sodium ion was available for potassium exchange in the distal tubules. The proximal tubular effect of furosemide,[30] however, overcame the action of aldosterone at this site[21,31] and thereby permitted aldosterone to enhance potassium secretion in distal tubules.[32,33] As a result, the serum potassium concentration decreased promptly and the paralysis remitted (Fig. 2). The distal tubular action of spironolactone, therefore, seems to act in the direction of potassium retention and hyperkalemia, while its proximal tubular effect may promote potassium excretion.

Experimental data indicate that in hyperkalemia muscle cells are partially depolarized and they are less excitable.[4,34] The membrane potential is proportional to the logarithm of the intracellular and extracellular potassium concentration ratio

$58 \log \frac{K\ int}{K\ ext}$.[35] Because of the frequent episodes of weakness in the presence of a nonincreasing hyperkalemia, loss of the intracellular potassium may decrease the value of this ratio, i.e., partial depolarization. Thus, in the last stage of spironolactone treatment, the frequent episodes of muscle dysfunction may be attributed to relative hyperkalemia due to progressive diuretic intracellular potassium loss. The diuretic interventions leading to a decrease of the serum potassium level restored equilibrium at a lower level and abolished paralysis.

Summary

Intermittent hyperkalemic weakness and flaccid paraplegia were observed during chronic spironolactone treatment in a case of refractory ascites due to cardiac cirrhosis. The patient was treated also with steroid and there was no azotemia. The increase of potassium excretion by treatment with a combination of aldosterone, furosemide, and acetazolamide was temporarily advantageous because it diminished hyperkalemia and abolished paralysis. Renal and extrarenal influences are considered that may be involved in the regulation of serum potassium level during chronic treatment with spironolactone and its combination with diuretics.

REFERENCES

1. Berliner, R. W.: Use of modern diuretics, Circulation 33:802, 1966.
2. Edmonds, C. J., and Wilson, G. M.: The action of hydroflumethiazide in relation to adrenal steroids and potassium loss, Lancet 1:505, 1960.
3. Read, A. E., Laidlaw, J., Haslam, R. M., and Sherlock, S.: Neuropsychiatric complications following chlorothiazide therapy in patients

with hepatic cirrhosis possible relation t hypokalaemia, Clin. Sc. 18:409 1959
4. Radó, J P Hammer S. and Szilágyi, L.: Effective treatment of decompensated cir rhosis of liver by combined use of glucocorticoids and thiazide compounds together with mercurial diuretics mode of potentiation with special reference to collecting tubular action of chlorothiazide compounds, Magy Belorv Arch. 15 144 1962.
5. M nning R. T and Behrle, F C. Use of pironolactone in renal edema, J.A.M.A. 176 769 1961
6. Herman, E., and Radó J P F tal hyper kalemic paralysis associated with spironolac tone Observation on patient with severe renal disease and refractory edema, Arch. Neurol. 15 74, 1966.
7 Cohen, A. B. Hyperkalemic effects of triamterene, Ann. I t. Med. 65:521 1966.
8. Finch, C A., and Marchand, J F Cardiac arrest by the action of potassium, Am. J M Sc. 206:507 1943
9 McNaughton R. A. and Burchell, H B Paralysis with potassium intoxication in renal insufficiency J.A.M.A. 145:481 1951
10. Sta bury S. W and Mahler R. F Salt wasting renal disease, Quart. J Med. 28:425 1959
11 Murphy R. V et al. Studies of sod'um and potassium metabolism in salt-losing nephritis, Arch. Int. Med. 90 750, 1952.
12. Read, A E. Salt loss chronic renal disease Brit. M J 1 1399 1956.
13. Mollaret, P Goulon, M and Tournilhac, M Contribution à l étude des paralysies vec hyperkaliémie, Rev Neurol. 99:241 1958
14 Mollaret, P Lähmungen bei Störungen des Kaliumstoffwechsels, München. med. Wchnschr 102:165 1960.
15 Mollaret, P Goulon M nd Tournilhac, M La problème des paralysies vec dyskaliémies, Presse Med. 67:2137 1959
16. B ll, G. M Carter A. B., and Low h. G Hyperpotassemic paralysis, Lancet 2:60, 1953
17 F w M L. and E er B W I termittent paralysis nd chronic adrenal insufficiency Ann. I t. Med 57:461 1962
18. Marks, L. J and Feit, E Flaccid quadriplegia, hyperkalemia and Addison disease, Arch. I t. Med 91:56, 1953.
19 Richardson, G. O and Sibley J C. Flaccid quadriplegia associated with hyperpotassemia, Canad. M A. J 69:504 1953
20. Mollaret, P Goulon, M and Tournilhac, M : Contribution à l'étude des paralysies avec hyperkaliémie, Rev Neurol. 98:341 1958.
21 Pollen, R. H nd Williams, R. H Hyperkalemic neuromyopathy in Addison s disease New England J Med. 263:273 1960.
22. Bell, H., Hayes, W L. and Vosburgh, J Hyperkalemic paralysis due to adrenal insufficiency Arch. I t. Med. 115:418, 1965
23. Drager G. A. Hammill, J F and Shy G. M Paramyotonia congenita Arch. Neurol. & Psychiat. 80:1 1958.
24 Armstrong F S. Hyperkalemic familial periodic paralysis (dynamia episodica hereditaria) Ann. Int. Med. 57:455 1962.
25 Vesin, P Late functional renal failure in cir rhosis with ascites: pathophysiology diagnosis and treatment, in Martini, G A., editor Aktuelle Probleme der Hepatologie Stuttgart, 1962 Georg Thieme Verlag, pp. 98-109
26. Vesin, P Traverso, H Hirsch-Marie H and Cattan, R. L insuffisance rénale circulatoire spontanée d cirrhotique. Son évolution, Sem hôp. Paris 38:3598, 1962.
27 Gantt, C. L., and Ecklund, R. W Significance of aldosterone antagonism in the treatment of edema and ascites, Am. J Med. 33:490, 1962.
28. Radó, J P Takó, J H mmer Ch., and Szilagyi, L. Über die Wirkung von Aldosteron und Aldacton-A auf die verschiedenen Abschnitte der Nierent bull beim C shing-Syndrom mit Polyurie, Ztschr ges. Inn. Med. 20:521 1965.
29 Hierholzer K., Wiederholt M and Stolte H Hemmung der Natrium reabsorption im proximalen und distalen Konvolut adrenalektomierter Ratten, Pflügers Arch 291:43 1966.
30. Radó, J P Takó, J and Szabó, T Site of action of furosemide, J Clin. Pharmacol. J New Drugs 7 142 1967
31 Davidson D G Levinsky N G., and Berliner R. W Maintenance of potassium excretion despit reduction of glomerular filtration rate during sodium diuresis, J Clin. Invest. 37:548, 1958.
32. Schedl, H P nd Bartter F C. An explanation for and experimental correction of the bnormal water diuresis i cirrhosis, J Clin. Invest. 39:248 1960.

Review

The mitral complex

Interaction of the anatomy, physiology, and pathology of the mitral annulus, mitral valve leaflets, chordae tendineae, and papillary muscles

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Mitral stenosis and mitral regurgitation have captured and sustained the interest of physicians since John Mayow described constriction of the mitral orifice in 1668[1] and James Hope separated mitral regurgitation from mitral stenosis in 1832. Though a great wealth of literature has detailed the physical signs and clinical manifestations of these entities, only scant attention has been given to the separation of the various mechanisms by which obstruction or regurgitation can occur at the mitral orifice.

The anatomic regulation of the blood flow across the mitral orifice depends on a complex interaction between the mitral annulus, the mitral valve leaflets, the chordae tendineae, and the papillary muscles. In the normal heart this mitral complex (Fig. 1) is capable of closing the mitral orifice without permitting any regurgitation of blood during ventricular systole, yet still opens widely enough during diastole to allow ventricular filling without a detectable pressure difference across the mitral orifice. This intricate structure contrasts with the relatively uncomplicated aortic valve mechanism which does not require such an elaborate framework for opening and closing the aortic orifice.

The tissues of the mitral complex are not unique to that location and therefore it could be anticipated that the mitral complex may be assaulted by any disease that can attack these tissues elsewhere in the body. Because the proper function of the mitral complex depends on the precise integration of each of its components, then serious hemodynamic consequences can occur even though the effect of the disease may be limited to just one part. Accordingly, it is logical to search for and to discuss the disease processes that attack the four parts of the mitral complex.

The purpose of this review is to emphasize the common embryologic origin and the functional anatomic relationships of the mitral complex and to discuss the great array of local and systemic diseases which may interfere with the proper functions of the mitral complex, producing obstruction or regurgitation at the mitral orifice.

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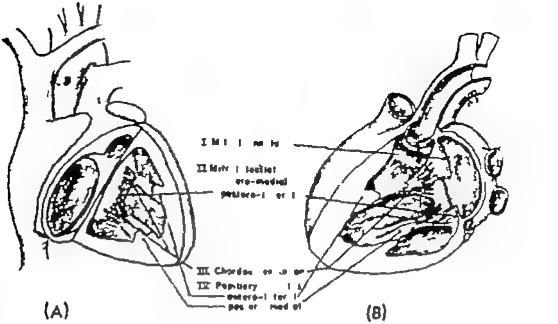

Fig. 1. The four components of the mitral complex. *A*, Frontal view. Right ventricle and ventricular septum removed. *B*, Left lateral view. Lateral wall of left atrium and left ventricle partially removed.

Embryology of the mitral complex

In the earliest stages of the development of the embryonic heart, the cardiac tube is lined by endothelium which is widely separated from an outer myoepicardial cover by an acellular fluid, the cardiac jelly. By about 34 days localized masses of mesenchymal cells have accumulated within the cardiac jelly and encircle the common atrioventricular canal. These masses protrude at two locations, superiorly and inferiorly, into the lumen of the embryonic heart as the superior and inferior endocardial cushions. When these endocardial cushions fuse in the midline the freely communicating chambers are then divided into a left and a right atrioventricular canal. The superior and inferior endocardial cushions also contribute to the formation of the atrioventricular valves, the lower atrial septum, and the membranous ventricular septum.[8-11]

By the seventh week the superior and inferior endocardial cushions have fused together uniting with the interventricular and interatrial septum to divide the heart into four chambers communicating only through the foramen ovale. By the eighth week, thick blunt tabs of valvular tissue arise from the fused superior and inferior endocardial cushions and from the lateral aspect of the endocardial cushion providing a ring of tissue projecting into the left A-V orifice. This tissue is anchored on its undersurface by considerable trabecular muscle to the ventricular wall. The valvular tissue then becomes more defined by absorption and undermining. The muscular trabecular connections to the apex of the valve are transformed into fibrous tissue, the chordae tendineae. The muscular connections from the chordae tendineae to the ventricular wall remain as the papillary muscles. The valve leaflets, which at one time are almost completely muscular tissue, are invaded and replaced almost entirely by collagen.[8-11]

The anteromedial mitral leaflet then has a dual origin, $^2/_3$ contributed by the superior and $^1/_3$ by the inferior endocardial cushion. The posterolateral leaflet originates entirely from the endocardial cushion tissue of the lateral ventricular wall. The chordae tendineae and the papillary muscles are derived from trabecular muscle which was originally continuous with the entire undersurface of the valve but through considerable thinning and undercutting eventually retain a contact only at or near the edge of the valve.

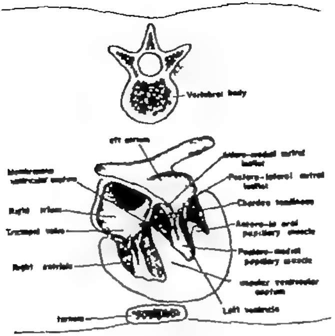

Fig. 2 Transverse section through the heart at approximately the third intercostal space illustrating the relationship of each of the cardiac chambers to each other and the orientation of the mitral orifice within the left heart. *R*, Right; *L*, left.

Anatomy of the mitral complex

General concepts of cardiac anatomy. Comprehension of the anatomic relationships of the heart has been hampered by the ingrained misleading designation of the heart as a "right-sided" and "left-sided" structure. As can be readily appreciated in Fig. 2, the plane of the interventricular and interatrial septa is at a 45° angle from a line passed from the mid-sternum through the spinal column.[22] This oblique position places the right ventricle anteriorly and just under the sternum with the right atrium forming the right lateral cardiac border. Since the longitudinal axis of the heart is tilted, the apex of the heart is more anterior than the base, placing the right atrium posterior as well as lateral and superior to the right ventricle.

The left ventricle comprises the apex and left border of the heart and is posterior as well as lateral to the right ventricle. The longitudinal axis of the left ventricle and therefore the mitral orifice then faces more laterally than anteriorly.[22] The left atrium is the most posterior chamber and is positioned superiorly, posteriorly, and to the right of the left ventricle.

Anatomy of the annulus fibrosus. The fibrous skeleton of the heart provides a relatively fixed collagenous framework for the attachment of the valvular tissue and the atrial and ventricular muscle.[13-15] Viewed from above with the atria removed (Fig. 3), the fibrous skeleton appears as several adjoining rings around a central fibrous core, the central fibrous body. Extending posteromedially from the central fibrous body is the right fibrous trigone which is enclosed by a triangle formed by the anteromedial mitral leaflet on the left, the septal tricuspid leaflet on the right, and the posterior aortic cusp in front. In addition, the right fibrous trigone is continuous with the membranous ventricular septum which extends inferiorly and anteriorly below the aortic cusps.[13]

The left fibrous trigone is thinner than the right fibrous trigone and extends anteriorly from the right fibrous trigone curving to the left between the left coronary aortic cusp and the anteromedial

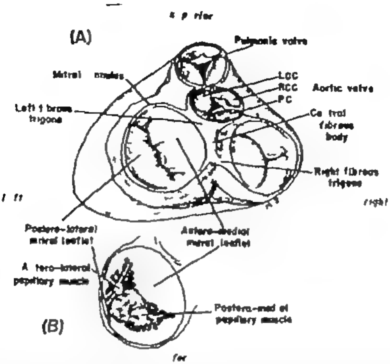

Fig 3 A Superior view of the base of the heart with atria removed The interconnecting rings of the fibrous skeleton are demonstrated. The mitral orifice is shown in systole to illustrate the anteromedial and posterolateral leaflets as they balloon upwards and together *LLC* Left coronary cusp *RCC* right coronary cusp and *PC* posterior cusp. *B* View of the isolated mitral orifice during ventricular diastole from above with atria removed to show anterolateral and posteromedial positions of the papillary muscles and the relative size of the mitral leaflets

mitral leaflet. From the left and right fibrous trigone fibroelastic tissue continues around the circumference of the atrioventricular orifices. These rings of supportive tissue are the annuli fibrosi to which the valvular tissue is affixed The annulus fibrosus of the mitral orifice measures from 8 to 12 cm in circumference at autopsy however with systole the surrounding deep bulbospiral muscle may contract the circumference considerably [20] The anteromedial third of the annulus fibrosus is continuous with the entire left coronary aortic cusp and with $^1/_2$ of the posterior (noncoronary) aortic cusp The remaining $^2/_3$ of the annulus fibrosus completes the formation of the ring extending laterally from the left fibrous trigone in front around to the right fibrous trigone posteromedially This part of the annulus may be incomplete or poorly defined

Anatomy of the mitral leaflets The mitral valve is suspended between the mitral *annulus* above and the two papillary muscles below (Fig 1) This mobile fibroelastic tissue completely surrounds the mitral orifice providing a *cone-shaped funnel* which is approximately 1 cm longer in circumference at its junction above with the annulus fibrosus than at its free edge below [15,24]

Both the atrial and ventricular aspects are lined by glistening slightly opaque endocardium Anterolateral and posteromedial indentations into this cone of tissue divide the cone into *anteromedial and* posterolateral leaflets. These indentations never dip as deeply as the valve ring leaving some bridging "commissural" tissue between the two *major* leaflets. Occasionally this commissural tissue may be prominent enough to *form an accessory* leaflet

The anteromedial mitral leaflet is roughly triangular in shape with the base of the triangle attached to the annulus fibrosus and its apex extending hinge-like into the left ventricular cavity From apex to basilar attachment the anteromedial leaflet may vary from 1 8 to 3.4 cm and is at

most twice the height of the posterolateral leaflet.[15-17] Its basilar length varies from 2.4 to 4.5 cm.[16] On its atrial surface the entire length of the base of the anteromedial leaflet is firmly attached to the annulus fibrosus and is continuous with the atrial endocardium. On its ventricular aspect, however, its base is fixed to muscle at only two places. The posterior third is fastened to the summit of the most posterior extent of the muscular interventricular septum directly beneath the middle of the noncoronary aortic cusp.[20] It then stretches anteriorly and obliquely to the left where it is attached at the anterolateral commissure to the anterolateral left ventricular free wall. The base between these two muscular attachments is continuous with the fibrous supportive tissues of the noncoronary (posterior) and the left coronary aortic cusps lying above.[7]

This broad curtain strung from the top of the posteromedial ventricular septum to the anterolateral ventricular wall separates the left ventricular cavity into an inflow and an outflow tract. The inflow tract, formed by the mitral annulus, the mitral valve leaflets, and the chordae tendineae, directs the atrial blood entering the left ventricle inferiorly, anteriorly and to the left. The outflow tract, consisting of the ventricular surface of the anteromedial leaflet, the muscular and membranous septum, and the left ventricular free wall, orients the left ventricular outflow superiorly, posteriorly, and to the right at an angle of 90° to the inflow tract.[12] The anteromedial leaflet then has intimate associations with the left atrium, the base of the aorta, the muscular septum, and the left ventricular wall which permit efficient separation of the left ventricle into a receiving and an expelling chamber in the normal heart.

The posterolateral mitral leaflet is quadrangular in configuration, resembling a long banner, being much longer than it is broad. Its base varies from 2.3 to 4.1 cm. in length with a height from 0.8 to 2.5 cm., and is firmly fastened along its entire length to the mitral annulus at the top of the free wall of the left ventricle. The posterolateral leaflet encircles about ⅗ of the mitral orifice extending from the anterolateral left ventricular wall to the junction of the posterior left ventricle and the muscular ventricular septum. The combined surface area of both mitral leaflets is two times greater than the area of the mitral orifice permitting a large area of coaptation between their vertically directed lower borders. Though the contribution to valve closure differs between the two leaflets, improper function or loss of substance of either leaflet may allow severe mitral regurgitation.[16]

Anatomy of the chordae tendineae. From the tip of each papillary muscle strong cords of fibrous tissue, the chordae tendineae, radiate upward attaching to the corresponding half of both the anteromedial and posterolateral mitral leaflets. Immediately after departing from the papillary muscle, the chordae make extensive cross connections between each other. On the atrial surface of the anteromedial leaflet, the chordae attach into a fibrous band running along the entire free edge sparing only the tip of the apex and giving the valve border a scalloped appearance. These are first order chordae and are less than 0.1 cm. thick. On the ventricular side, chordae attach to and course within the valvular tissue a few millimeters deep to the free edge and are known as second order chordae.[13, 4, 20, 22]

The chordae tendineae are similarly attached to the entire edge of the posterolateral mitral leaflet sparing just the center. The posterolateral leaflet differs from the anteromedial leaflet as it also has third order chordae crossing from the ventricular wall to the undersurface of the body of the leaflet.[16] The body of the anteromedial leaflet is free of third order chordal attachments and therefore is more mobile than the posterolateral leaflet. Often the chordae attaching nearest the apex of the leaflet are stouter than the others.[21-4]

The numerous cross-connections between the chordae, the chordal attachments to almost the entire free leaflet edge, the stout central chordae, and the second order chordae to the anteromedial leaflet offer a strong and well-distributed support against the force generated by left ventricular systole.

Anatomy of the papillary muscles. There are usually two papillary muscles in the left ventricle which may be bifid, trifid

or infrequently a row of muscles.[4,22] The papillary muscles originate at the junction of the middle and apical thirds of the left ventricular wall as a component of the interlacing trabeculae carneae.[23,24] They are oriented parallel to the left ventricular wall to which they are usually attached almost to their peak by crossing muscle bundles and thread like bands. The two papillary muscles are located at the anterolateral free wall and diagonally across the ventricular cavity at the junction of the posterior free wall and the muscular ventricular septum.[24] They jut into the upper third of the ventricular cavity directly below the commissural tissue at the anterolateral and posteromedial left ventricle.

Innervation of the mitral complex. Animal studies demonstrate a wide distribution of afferent nerves in the atrioventricular valves.[27,28] Fine medullated fibers course near the basal attachments of the valves or beneath the endocardium on the atrial aspect of the valves and join forming nerve plexuses. These nerves are in intimate contact with similar nerve fibers that run within the chordae tendineae to merge with the endocardial nerve plexuses around the papillary muscles. Their function is obscure, however, they may be sensitive to regional pressure or stretch changes along the valves and provide a more precise local control of the leaflets and the papillary muscles.[27] Since the valves contain both nerve and muscle, they would appear to have the capability of self initiated movement which might play an important part in valve opening and closure.[29]

The left ventricular papillary muscles are innervated by radiations of the left bundle branch.[30] The posterior radiation divides earliest from the A-V bundle at the posterior margin of the membranous ventricular septum. It then courses beneath the endocardium of the muscular ventricular septum posteromedially to enter the posteromedial papillary muscle. The anterior radiation of the left bundle is formed when the main bundle bifurcates into the right bundle branch and the anterior radiation of the left bundle branch at the level of the junction of the right coronary and noncoronary aortic cusps. The anterior division passes anteriorly and obliquely to terminate in the anterolateral papillary muscle. This pattern of innervation permits the papillary muscles to be stimulated prior to the contraction of the deeper muscles drawing the mitral leaflets together and downward facilitating valvular closure before ventricular ejection.

Blood supply of the mitral complex. The occurrence and importance of blood vessels in the valvular tissue is still unclear. In many hearts, ramifying interconnecting arterioles form a network of fine vessels beneath the endocardium of the atrial surface.[31-33]

The arterial branches supplying the anteromedial mitral leaflet originate from Kugel's artery.[34,37] This artery arises from the proximal left circumflex or proximal right coronary artery and courses from anterior to posterior at the base of the interatrial septum. As it passes within 1 cm of the anteromedial leaflet, small arteries descend to the base of the leaflet and either form an arch or enter into the leaflet. A specific artery to the posterolateral mitral leaflet has not been identified, but the blood supply probably originates as a branch of the left circumflex artery.

The blood supply to the papillary muscles is well delineated.[36,37] The anterolateral papillary muscle receives its blood from the left coronary artery, particularly the marginal branches of the circumflex and the diagonal branches of the anterior descending artery.

The posteromedial papillary muscle has a variable blood supply depending on which artery courses over the posterior heart. In some cases, this is mainly the posterior distribution of the right coronary artery with smaller contributions from the left circumflex distribution to the posterior wall. In other cases, the left circumflex artery is the main provider. The anterolateral papillary muscle seemingly has the more lavish blood supply since it is infarcted less frequently than the posteromedial papillary muscle.

As these major vessels course over the epicardium, small vessels take their origin and dip into the myocardium. Some of these divide into fine vessels in the outer four fifths of the myocardium, while

others continue to the subendocardium including the papillary muscles, where they terminate in large caliber arcades, providing a network of subendocardial anastomoses.[31,34] Blood vessels have been demonstrated in the chordae tendineae originating either from the valve above or from the papillary muscle below.[32-34]

Physiology of the mitral complex

The mitral valve opens and seals the mitral orifice in response to a dynamic interaction of pressures on its atrial and ventricular surfaces. Since these pressure changes are the consequence of a great array of influences on the atrium and the ventricle, then the exact timing of mitral valve opening and closure in the cardiac cycle must take into account these variables (Fig. 4).

The "a" wave of the left atrial pressure curve is produced by left atrial systole.[39,40] The peak of the left atrial "a" wave may be elevated by sympathetic stimulation to the left atrium,[41] obstruction to forward flow due to mitral stenosis or with reduced ventricular compliance as in left ventricular hypertrophy,[42,43] an increased mean left atrial pressure prior to atrial systole,[44] and an increased left ventricular end-diastolic pressure. Vagotonia,[41] increased

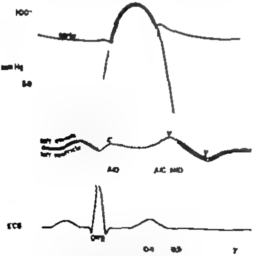

Fig. 4. Diagram of the cardiac cycle showing the pressure curves of the left atrium, left ventricle, and aorta with simultaneous ECG. *MC* and *MO*, Mitral valve closure and opening. *AO* and *AC*, aortic opening and closure.

compliance of the left atrium,[43,44] and regurgitant flow back into the pulmonary veins[39,47] may decrease the "a" wave peak. Left atrial relaxation following atrial systole together with the decrease in left atrial volume is reflected by a fall from the "a" wave peak. The "z" point indicates atrial pressure at the onset of ventricular contraction. Its temporal relationship to left atrial systole depends on the left ventricular end-diastolic pressure.[44] The "z" point is the last moment that the atrium and ventricle are in communication and reflects the left ventricular end-diastolic pressure.[39] The mitral valve closes during this period when the heart is in sinus rhythm.

Numerous theories have been proposed to explain the exact mechanism of mitral valve closure.[34,48,61] Though each of the following theories might theoretically explain the closure of the mitral valve, it is possible that each contributes importantly in sequence to normal valvular closure. When one mechanism is faulty or absent, then a subsequent event assumes greater importance in approximating and maintaining a closed mitral valve.

1. As the pressure wave of the left atrial systole is propagated into the left ventricle, the left ventricular pressure is abruptly greater than the pressure within the relaxing atrium. This rapid reversal in the atrioventricular pressure difference closes the mitral valve.[48-52] This requires an optimal timing of atrial systole with ventricular systole so that the valves do not reopen.[49]

2. The force of atrial contraction produces a jet stream across the mitral orifice. The jet stream creates an area of negative pressure which exerts a suction effect on the valves pulling them together.[53] In addition, eddy currents produced by the sudden movement imparted to the ventricular blood by the atrial jet exert a force on the ventricular surface of the leaflets further aiding valve closure.

3. The papillary muscles contract at the beginning of systole before the rest of the myocardium contracts pulling the leaflets deeper into the left ventricular cavity in a vertical direction.[33,34] The chordal contribution to both leaflets from each papillary muscle draws the leaflets together

4 During isovolumetric ventricular contraction the rising intraventricular pressure balloons the leaflets upward sealing them together.[31,33,35-37]

In addition to these effects, the musculature surrounding the mitral orifice further contributes to valve closure by contracting and reducing the mitral orifice.[33,37,40] Contraction of muscle within the mitral leaflets may aid in valvular closure.[39]

It has been repeatedly demonstrated that atrial systole alone can approximate the mitral leaflets.[41-50] An improperly timed atrial contraction as in A V dissociation or premature ventricular contractions, or loss of atrial systole as in atrial fibrillation may permit some mitral regurgitation.[45-48] On the other hand it is equally clear that valve closure can occur without mitral regurgitation in the presence of these arrhythmias.[49] Without atrial systole the rise in the left ventricular pressure and the contraction of the papillary muscles assume more importance.

Isovolumetric contraction begins with the initial rise in left ventricular pressure and ends with the opening of the aortic valve. The blood volume propelled into the left ventricle by atrial systole increases the length of the end-diastolic left ventricular fiber producing an increased force and velocity of left ventricular contraction.[51,44] This resultant increased velocity of left ventricular contraction abbreviates the isovolumetric contraction period.

During diastolic filling the left ventricle elongates, becoming roughly cylindrical in configuration. The force exerted on the mitral ring by the contraction of the papillary muscles and the trabeculae carneae pulls the atrioventricular junction toward the ventricular apex shortening the longitudinal axis of the left ventricle.[29,33] Since the rest of the myocardium has not yet contracted and the blood volume has not changed the shortening of the longitudinal axis of the ventricle results in a bulging of the left ventricular walls and a more spherical configuration.[68,70]

The descent of the A V junction enlarges the left atrium and the left atrial pressure falls as seen in the "x" descent.[23,68] Atrial relaxation may also contribute to the "x" descent.[71] The downward fall of atrial pressure is transiently interrupted by a positive "c" wave as the mitral leaflets bulge into the left atrial cavity as they oppose the rising ventricular pressure.[23,68,71] During ventricular systole the continued contraction of the papillary muscles holds the chordae tendineae taut and the mitral leaflet edges together as the rising interventricular pressure billows the leaflets upward into the left atrium.[72,73]

The phase of isovolumetric contraction is succeeded by rapid ejection as the left ventricle contracts from apex to base. When left ventricular pressure exceeds aortic pressure the aortic valve opens.

The descent of the base of the heart and resultant lowering of the atrial pressure accentuates the pressure gradient from pulmonary veins to left atrium and accelerates the central venous return.[68,74] During the latter part of ventricular ejection, left atrial pressure rises as the pulmonary venous inflow accumulates. This rise in atrial pressure inscribes the "v" wave which reaches its peak 0 01 to 0 10 second prior to mitral valve opening.[23,68,71,75,76] This slight decline in left atrial pressure before mitral valve opening is poorly understood.

When atrial pressure exceeds ventricular pressure the mitral valve opens.[44] The time of the mitral valve opening in relation to the second heart sound is influenced by the rate of ventricular relaxation the pressure difference between the left atrium and the end-systolic left ventricular pressure, and the mobility of the mitral valve.[77,78]

After reaching a peak, the "v" wave descends as the "y" descent as the atrial blood rapidly enters the left ventricle.[73] This rapid inflow of atrial blood again elongates the left ventricle returning the mitral annulus and the mitral leaflets to their previous distance from the apex.[1] This is the annular ascent and its highest point is reached at the end of the rapid filling wave. The ascent of the mitral ring reduces the size of the mitral orifice and therefore the rate of diastolic filling. The "y" descent then decelerates or may start to rise.[69]

Diseases of the mitral complex

Diseases of the annulus fibrosus The annulus fibrosus surrounding the mitral

orifice is composed of fibroelastic tissue that is vulnerable not only to the repetitive strains of valvular and muscular pull but also to several diseases that commonly affect the mitral leaflets.

Calcification of the mitral annulus may be found as frequently as 10 per cent of unselected autopsies, most commonly after 60 years of age and in women. The calcification involves the posterior portion of the annulus to the greatest degree, however the entire annulus may be involved.[38] Though this calcification may be an incidental autopsy finding, significant consequences may occur. The normal sphincteric movement of the annulus that aids in valve closure may be impaired.[39,40] The calcific masses may encroach upon the mitral orifice and obstruct blood flow. Massive calcification can bind down the leaflets, displace the chordae tendineae, or protrude beneath the leaflets preventing downward movement.[39] Both mitral stenosis and mitral regurgitation can result. The calcification may extend into other parts of the fibrous skeleton of the heart disrupting atrioventricular conduction.[41-43]

The etiology of the calcium deposition is unclear. Degeneration with secondary calcification related to the many years of stress on the fibrous skeleton by the muscular contractions is frequently postulated.[41] Calcification of the annulus may also be associated with rheumatic heart disease, coronary atherosclerosis, and hypertensive cardiovascular disease.[42-44]

The mitral ring may be damaged by abscesses,[37] by rheumatic inflammation,[44] and by rheumatoid granulomata.[46] It is unlikely that the ring can become greatly enlarged by severe left ventricular dilatation alone. A more likely explanation for the mitral regurgitation seen in severe dilatation of the left ventricle is the malalignment of the papillary muscles pulling in a horizontal rather than the usual vertical direction.[28]

EXAMPLE 1. An 85-year-old Caucasian woman was noted to have a heart murmur on an out-patient clinic visit. Her only symptom was mild shortness of breath on exertion. A chest film revealed a heavily calcified mitral annulus with minimal cardiomegaly (Fig. 5). There was no history of rheumatic fever, hypertension, or myocardial infarction. Physical examination has shown a normal apex impulse with a Grade 2 holosystolic murmur localized to

A B

Fig. 5. A, Calcified mitral annulus in anteroposterior projection (arrows). B, Lateral view.

the apex and a short mid-diastolic rumble. No opening snap or gallop sound has been heard

COMMENT. This elderly woman presents a fairly classic history for a calcified mitral annulus. Though the annulus is heavily calcified, only minimal hemodynamic impairment is evident in her history or physical examination. The fairly normal heart size and absence of a ventricular gallop suggest that her mitral regurgitation is not significant.

Diseases of the mitral leaflets. The normal mitral leaflets are able to open and close the mitral orifice quickly because of a remarkable mobility facilitated by attachments at only the basilar and apical aspects, a specific gravity approximating that of blood, a smooth surface minimizing friction, and by a large area of coaptation between vertically directed leaflets so that very little movement is necessary to allow an unimpeded flow of blood across the mitral orifice.[illegible]

A great array of diseases may alter the normal function of the mitral leaflets producing an obstruction to blood flow or permitting blood to regurgitate across the orifice. An immobile mitral valve is often unable to close and therefore, mitral regurgitation is often associated with significant mitral stenosis.

Mitral regurgitation may be the consequence of loss or contracture of valvular tissue, of incomplete or abnormal valvular development, of restriction of leaflet movement, or of an anomalous attachment of one or more leaflets. Rheumatic inflammation may contract and destroy valvular tissue and also fuse the commissures together preventing normal leaflet excursion.[illegible] Systemic lupus erythematosus[illegible] and infections[illegible] including syphilis[illegible] and polio[illegible] are other inflammatory disorders that may result in loss of valve tissue. The mitral valve may rupture from external, nonpenetrating trauma,[illegible] from direct damage such as a shrapnel wound[illegible] and spontaneously following exertion.

Incomplete valvular development may leave a cleft in the anterior or rarely the posterior leaflet.[illegible] Anterior leaflet clefts, usually with anomalous chordae tendineae, are often associated with a common atrioventricular canal;[illegible] however, occasionally other defects are present[illegible] or the cleft mitral leaflet is an isolated defect. Though the valvular tissue may be completely formed, the connective tissue structure may be abnormal. Thickening or scarring of the mitral valve, often with nodular excrescences, occurs in connective tissue disorders including the Ehlers-Danlos syndrome,[illegible] Hurler's syndrome,[illegible] Marfan's syndrome,[illegible] pseudoxanthoma elasticum,[illegible] and osteogenesis imperfecta.[illegible] Mitral stenosis and sometimes insufficiency may result. Leaflet redundancy, myxomatous changes in the leaflet and aneurysmal protrusion of the posterior mitral leaflet into the left atrial cavity during systole allowing mitral regurgitation also occur in Marfan's syndrome.[illegible] Congenital mitral regurgitation may be secondary to retraction of the leaflets, absence of the leaflets, redundancy of the leaflets, fusion of the commissures, and clefts or perforation of the leaflet.[illegible] Familial mitral regurgitation associated with deafness and skeletal abnormalities has been reported.[illegible] An anomalous attachment of the leaflet to the ventricular septum,[illegible] a more anterior position than usual,[illegible] or an Ebstein's malformation of the leaflets associated with corrected transposition of the great vessels may prevent the leaflet from moving into position of closure.[illegible]

Obstruction of the mitral orifice can occur when inflammation, fibrosis, or calcification impair normal valvular pliability, when the valve is congenitally deformed, and when tumors arise from the valve.

Rheumatic inflammation may produce thickening of one or more leaflets, adherence of the commissures, or in advanced stages a proliferative fibrosis fusing and immobilizing the leaflets, chordae tendineae, and papillary muscles into a rigid funnel.[illegible] Granulomatous inflammation from rheumatoid arthritis may scar the mitral leaflets.[illegible] Acute angioneurotic edema of the mitral valve producing obstruction of the orifice has been reported.

The mitral valve may also be thickened [illegible] endocardial

Systemic

occur in

rheumatic heart disease[158,159] bacterial endocarditis,[154,156] and rheumatoid arthritis.[67] With advancing age the collagen fibers in the valve become thicker and by the fifth decade calcification is frequently found.[158] Localization of the calcium to sites of maximum stress suggests that this may be related to degeneration.[158,160]

Isolated congenital mitral stenosis is uncommon but may be a part of the hypoplastic left heart syndrome.[61] The valve may exist only as a dimple with no communication between the left atrium and the left ventricle.[161,164] Other cases may show markedly thickened or undifferentiated leaflets, fusion of the commissures or a diaphragm instead of a valve.[67,73] Abnormal poorly-defined chordae tendineae usually accompany this type of malformation.[61] Tumors of the mitral valve usually arise on the atrial surface and impede blood flow across the orifice. The types of tumors reported include fibromyxoma,[75] fibroma,[77] fibrosarcoma lymphangioma,[79] endothelioma,[80] mixed cell sarcoma,[82] myxoma,[83-130] and chondrosarcomatous mesenchymoma.[84]

EXAMPLE 2. A 39-year-old Negro woman was well until January, 1964 when she coughed up blood and came to the Emergency Room. Murmurs of mitral stenosis and mitral regurgitation were heard and atrial fibrillation was documented on the ECG. Except for one additional episode of hemoptysis, she had only minimal limitation of activity until three days prior to admission when she became dyspneic at rest. This was succeeded by severe dyspnea and hemoptysis requiring admission.

Physical examination showed a gasping woman who was coughing up considerable amounts of blood. The pulse was 170 and irregular with a barely palpable systolic pressure of 70. The neck veins were engorged at 90 degrees. A parasternal heave was prominent. A faint systolic murmur was audible. No opening snap or diastolic murmur was heard.

Despite large doses of intravenous Digoxin, the heart rate did not slow and the patient became more hypotensive. Emergency bedside cardioversion was successful in converting her atrial fibrillation to a sinus rhythm with a rate of 105. Her systolic blood pressure immediately rose to 90 mm. Hg and she showed evidence of a dramatic clinical improvement. A diastolic rumble could now be heard. Her subsequent hospital course was uneventful. At operation two months later, a heavily calcified mitral valve that would barely admit a fingertip was found.

COMMENT. When the mitral obstruction is severe, the cardiac output to a great extent is dependent on a long diastolic filling period of the ventricle. When the diastolic filling period is abbreviated by tachycardia, the cardiac output may decrease and the left atrial pressure rise considerably. Hemoptysis, pulmonary edema, and hypotension may be the consequences. Atrial systole assumes great importance in augmenting diastolic filling and decompressing the left atrium, particularly at fast heart rates.

This patient was critically ill until her heart rate was slowed and the benefit of atrial systole was added. Emergency cardioversion was the only method that was effective in slowing the heart rate. At rapid heart rates the diastolic murmur may be difficult to time or inaudible as in this patient presenting a difficult diagnostic problem if the patient has not been previously diagnosed. Careful auscultation at a slower rate is mandatory in any patient with unexplained atrial fibrillation.

Diseases of the chordae tendineae. By their attachments to almost the entire free edge, the chordae tendineae allow the body of the mitral leaflets the mobility to balloon upward and against each other while evenly distributing the pressures exerted by ventricular systole on the leaflets.[38] The contribution of each of the threadlike chordae tendineae is emphasized by the severe mitral regurgitation produced experimentally by severing just one of the first order chordae.[40]

Diseases involving the chordae tendineae may result in hemodynamic alterations by several mechanisms. Shortened or fused chordae may allow mitral regurgitation by restricting the upward movement of the leaflets and thereby preventing mitral closure or they may cause obstruction of the mitral orifice by pinioning the mitral leaflets in the pathway of diastolic flow into the ventricle. The most common disease which shortens, thickens, and fuses the

chordae together in rheumatic heart disease.[illegible]

Thickened or poorly defined chordae tendineae may also occur in isolated congenital mitral stenosis,[illegible] isolated congenital mitral insufficiency,[illegible] Hurler's syndrome,[117] Marfan's syndrome,[illegible] the Ehlers-Danlos syndrome,[illegible] A-V cushion defect,[illegible] the hypoplastic left heart syndrome,[illegible] the parachute mitral valve complex,[117] with a supravalvular ring of the left atrium,[illegible] and the carcinoid syndrome.[illegible]

The chordae tendineae may rupture creating significant mitral regurgitation depending on the number torn and their location. Rupture of a chordae may be produced by bacterial endocarditis,[illegible] trauma,[illegible] rheumatic heart disease,[illegible] Marfan's syndrome,[illegible] the Ehlers-Danlos syndrome,[illegible] and rarely myocardial infarction.[illegible] Chordal rupture in rheumatic heart disease may be secondary to healed bacterial endocarditis. Distortion of the valve may be contributory by altering the normal equal distribution of pressure to all of the chordae. This may subject some chordae to a greater pressure than others, precipitating a chordal rupture. Sometimes an apparently normal chordae ruptures.[illegible]

The chordae may be elongated and redundant in Marfan's syndrome and in the Ehlers-Danlos syndrome permitting mitral regurgitation when the leaflet flops into the left atrium during systole.[illegible]

Anomalous chordae arising from an unusual location such as the ventricular septum or inserting abnormally into the body of the mitral leaflet may restrict the excursion of the leaflet and allow mitral regurgitation. Anomalous chordae reaching from the ventricular septum to the border of the cleft leaflet occur frequently in A-V cushion defects.[illegible] They are also present in corrected transposition of the great vessels[illegible] and in isolated congenital mitral regurgitation where the chordae may be anomalous or absent.[illegible]

EXAMPLE 3. A 67-year-old Negro woman with hypertension since 1949 was asymptomatic until December, 1965, when she awoke abruptly with a substernal tightness, wheezing, and severe dyspnea. Examination at that time showed a holosystolic apical murmur and pulmonary congestion. There was normal sinus rhythm. ECG's showed no evidence of myocardial infarction.

She did fairly well on digitalis and diuretics until February, 1967, when her rhythm changed to atrial fibrillation. Since that time she has been in severe congestive heart failure intractable to therapy.

Examination currently reveals a thrusting, broad systolic apical impulse, and a palpable ventricular filling wave. A Grade 5/6 harsh holosystolic murmur is present at the apex radiating to the spine and well heard on top of the head (Fig. 6).

COMMENT. Though the exact etiology of this patient's mitral regurgitation is not

Fig. 6. Phonocardiogram demonstrating holosystolic murmur recorded [illegible] left sternal border [illegible], left scapula, and top of the head. All recordings [illegible] 100 cycles per second upper frequency [illegible] paper speed 100 mm. per second. S.M., systolic murmur; ECG, [illegible] apexcardiogram [illegible] mitral opening [illegible] rapid filling [illegible]

clear, either a ruptured chordae tendineae or papillary muscle is suspected. A chordal rupture is rare from a myocardial infarction; however it can occur.[10] The radiation of the murmur suggests that the injured chordae tendineae or papillary muscle attaches to the anteromedial mitral leaflet allowing the leaflet to evert into the left atrial cavity and deflect the regurgitant bloodstream posteriorly.[10] Recently, the murmur on top of the head was found secondary to a ruptured chordae tendineae of the anteromedial mitral leaflet in the majority of cases.[10] The sudden increase in her congestive heart failure when her rhythm changed to atrial fibrillation again underlines the importance of atrial systole.

Diseases of the papillary muscles. Since the papillary muscles are a specialized projection of the trabeculae carneae, they are subject to all of the diseases that may affect the rest of the ventricular muscle. Their unique muscular function of participating in the sequence of valvular closure and in preventing the leaflets from everting into the left atrium under the stress of ventricular systole makes papillary muscle integrity and proper function of critical importance to the entire heart.

Their alignment parallel to the ventricular wall at the junction of the apical and middle third of the ventricle pulls the mitral leaflets together and downward with contraction. If this architectural relationship is disturbed by a malalignment of position of the papillary muscles, mitral regurgitation may result. This is seen in endocardial fibroelastosis where the papillary muscles may originate higher on the ventricular wall than usual,[8,197] in dilatation of the left ventricle where the papillary muscles lose their vertical orientation to the leaflets as they ride higher on the dilated ventricular wall and pull in a more horizontal direction,[8] in idiopathic hypertrophic subaortic stenosis where the asymmetrical contraction of the hypertrophied ventricle distorts the direction of the papillary muscle pull,[8] in anomalous mitral arcade where a bridge of fibrous tissue from the papillary muscles to the leaflets and anomalous or absent chordae tendineae restrict normal leaflet mobility,[198] and in the carcinoid syndrome where the papillary muscles and chordae may be bound down to the ventricular wall and their normal movements restricted by fibrous tissue.[199] In congenital mitral stenosis, the papillary muscles may be rudimentary or absent.[88,169]

Papillary muscle fibrosis, infarction or rupture may result from myocardial infarction,[200-211] abscess,[212] polyarteritis,[213] syphilis,[11] trauma,[189,214] and aortic stenosis.[11] Mitral regurgitation resulting from papillary muscle dysfunction secondary to ischemia may be the presenting sign of an anomalous coronary artery in an adult.[217,11] By far the most common etiology is ischemia secondary to coronary artery disease with a necropsy incidence of scars or infarction of the papillary muscle in 25 per cent of 420 consecutive autopsies.[218] The incidence of involvement is greatest for the posteromedial papillary muscle since its blood supply is more variable and at a longer distance from the coronary ostia than the anterolateral papillary muscle.[222] This is also true in aortic stenosis as the posteromedial papillary muscle may be atrophied or scarred because of poor coronary filling or the adverse effects of the increased intraluminal pressure collapsing the intramyocardial vessels.

EXAMPLE 4. A 39-year-old Negro man was admitted to the hospital after a recurrent substernal indigestion type of pain lasting five days and shortness of breath. There was no previous history suggesting heart disease, hypertension, or diabetes.

On admission, he was hypotensive and in florid pulmonary edema. The neck veins were distended at 90 degrees. No murmurs were heard. An atrial gallop was palpable and audible. Despite digitalis, morphine, and phlebotomy, he subsequently had cardiac arrest and died shortly after admission.

At autopsy, a ruptured anterolateral papillary muscle was found with extensive infarction of the free left ventricular wall. There was moderately severe atherosclerotic changes of the left anterior descending coronary artery.

COMMENT. The abrupt loss of papillary muscle support to the anteromedial mitral leaflet due to infarction emphasizes the importance of papillary muscle integrity as well as the tragic consequences that

may occur when the usual adaptation to chronic mitral regurgitation is circumvented The left atrium is suddenly subjected to a sudden increase in atrial volume and pressure.[31,139,181] This volume and pressure may be transmitted directly to the lungs and pulmonary edema may result. *In addition cardiac output is acutely* diminished by the diversion of the ventricular systolic output and hypotension ensues.

The frequent finding of an atrial gallop by palpation and auscultation in many cases of acute mitral regurgitation suggests that an augmentation of ventricular filling by atrial systole is a compensatory mechanism helping to increase the cardiac output and decrease atrial pressure.[330] The atrial contribution to ventricular filling may be impaired however because of a compromised atrial blood supply previous or acute atrial disease or an arrhythmia. Extensive infarction or a physiologic aneurysm of the left ventricular muscle may limit the ability of the left ventricle to increase stroke volume If the systemic vascular resistance is elevated as for example may occur in an acute myocardial infarction or secondary to vasopressor agents, then more mitral regurgitation may result.[331,332]

Absence of the murmur of mitral regurgitation is uncommon but occasionally the mitral regurgitation is not appreciated[89,220,256] In this severely ill patient, the tachypnea and râles may have masked the murmur The clinical picture and setting is often enough however to suggest a diagnosis of a papillary muscle or chordal rupture.

Summary

The unimpeded forward flow of blood across the mitral orifice is contingent upon a coordinated interaction between the mitral annulus the mitral valve leaflets, the chordae tendineae and the papillary muscles An understanding of the functional anatomy and physiology of each of these components of the "mitral complex" is clinically important for derangement of any part may produce obstruction to blood flow or allow mitral regurgitation The differential diagnosis then of mitral stenosis and mitral regurgitation can be functionally analyzed in terms of diseases of the mitral annulus, diseases of the mitral valve leaflets diseases of the chordae tendineae and diseases of the papillary muscles.

By this consideration of selective involvement of the mitral complex certain physical signs such as the late systolic murmur that may occur in papillary muscle dysfunction the murmur on top of the head heard with a ruptured chordae tendineae to the anteromedial mitral leaflet, the chordal snap of a redundant chordae tendineae, or the atrial gallop of an acutely ruptured chordae tendineae can be sought for in an attempt to differentiate clinically the possible etiology of the disease and its anatomic area of involvement This correlation of physical signs with the functional anatomy helps to provide an additional scientific basis to the physical examination.

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REFERENCES

1. Rolleston H. The history of mitral stenosis Brit Heart J 3 1 1941
2. Vander Veer J B Mitral insufficiency historical, and clinical aspects, Am J Cardiol 2:5 1958.
3. Van Mierop, L H S., Alley R. D Kausel, H. W and Stranahan, A The anatomy and embryology of endocardial cushion defects, J Thoracic & Cardiovas. Surg 43 71 1962.
4. Boyd, J D Development of the heart, *In* Hamilton, W F and Dow P editors Handbook of physiology section 2 (Circulation) vol. 3, Baltimore, 1965 The Williams & Wilkins Company p. 2511
5. Gasul, B. M Arcilla, R A and Lev M: Embryologic, pathogenetic, and pathologic considerations *In* Heart disease in children, Philadelphia and Toronto, 1966, J B. Lippincott Company p 15
6. Odgers, P N B The development of the atrioventricular valves in man, J Anat 73:643, 1939
7. Wilson, J G Embryology of the heart and major vessels, *In* Luisada A A editor Development and structure of the cardiovascular system, New York, 1961 McGraw Hill Book Co Inc p. 3
8. P L M H Endocardial cushion defects, Pediat. Clin North America 1011 1958.
9. Wakai, C S and Edwards J E: Developmental and pathologic considerations in persistent common atrioventricular canal Proc Staff Meet. Mayo Clin 31 45 1956.

10. P tten, B. M Human embryology New York and Toronto, 1953 The Blakiston Company p. 673
11 Keibel, F and Mall, F P M ual of human embryology Philadelphia and London, 1912, J B. Lippincott Company, p. 568.
12. W lmsley R., and W tson, H. The outflow tract of the left ventricle Brit. Heart J 28:435 1966.
13 Gra t, R. P Architectonics of the heart, Am Heart J 46:405 1953
14 Anson, B J The cardiovascular system. Human anatomy New York, 1966 McGraw Hill Book Co Inc., p. 644
15. Du Plessis, L. A., and Marchand, P The anatomy of the mitral val and its associated structures Thora 19:221 1964
16. Chiechi, M. A., Lees, W M and Thompson, R F nctional anatomy of the normal mitral valve, J Thoracic Surg 32:378, 1956.
17 Morris, E. W Some features of the mitral valve, Thorax 15 70 1960.
18 Davila, J C and Palmer T E The mitral valve Arch Surg 84 174 1962.
19 Licata, R. Anatom of the heart, Luisada, A., editor Development and structure of the cardiovascular system New York, 1961 M Graw Hill Book Co., Inc p 30
20. F ter R. W Persistent common atrioventricular canal, Circulation 32 120, 1965
21 Ed ards, J E and Burchell, H. B. P thologic anatomy of mitral insufficiency Proc. Staff Meet May Clin. 33:497 1958.
22. Rusted, I. E., Scheifley C. H. and Edwards, J E. Studies of the mitral valve. I Anatomic features of the normal mitral valve and associated structures, Circulation 6:825, 1952.
23. Van Der Spuy J C The functional and clinical anatomy of the m tral valve, Brit. Heart J 20:471 1958.
24. Brock, R. C The surgical and pathological anatomy of the mitral valve Brit. Heart J 14:489 1952.
25 Robb, J S and Robb, R. C.: The normal heart—anatomy and physiology of the structural units, Am Heart J 23:455 1942.
26. Estes, E. H J Dalton, F M., Entman, M. L Dixon, H. B II and Hackel, D B The natomy and blood supply of the papillary muscles of the left ventricle Am. Heart J 71:356, 1966
27 Volodschenko, A. A. Afferent innervation of trioventricular valves, Fed. Proc. (Suppl) 24:571 1965.
28. Williams, T H. Mitral and tricuspid valve innervation, Brit. Heart J 26:105 1964
29 Sonnenblick, E. H Napolitano, L. M Daggett, W M nd Cooper T An intrinsic neuromuscular basis for mitral valve motion in the dog, Circulation 21:9 1967
30. Lev M. The normal anatomy of the conduction system in ma nd its pathology in trioventricular block, Ann. New York Acad. Sc. 111:817 1964
31 Ritter S. A Gross, L., and Kugel, M A. Blood vessel in the valves of normal human hearts, Am. Heart J 3:433, 1928.
32. Bayne-Jones, S. The blood-vessels of the heart val es, Am. J Anat. 21:449 1917
33. Wearn, J T Bromer A. W and Zschiesche, L. J The incidence of blood vessels in h man heart valves, Am Heart J 11:22, 1936
34 Kerr W J and Mettier S. R. The circulation of the heart valves, Am. H art J 1:96, 1925
35 Kugel, M A. and Gross, L Gross and microscopical anatomy of the blood vessels in the alves of the human heart, Am. Heart J 1:304 1926.
36. Kugel, M A. Anatomical studies on the coronary arteries and their branches. I Arteria anastomotica auricularis magna, Am Heart J 3:260 1927
37 James, T N Anatomy of the coronary arteries health and disease Circulation 32 1020, 1965.
38. Estes, F H J Entman, M L. Dixon, H B., II and Haskel, D B The vascular supply of the left ventricular wall, Am. Heart J 71:58, 1966.
39 Brecher G A and Galetti, P M Functional anatomy of cardiac pumping n Hamilton, W F editor Handbook of physiology, section 2 (Circulation) vol 2, Baltimore 1963, The Williams & Wilkins Company p 759
40. Marshall, H W and Wood, E. H. Hemodynamic considerations in mitral regurgitation Proc Staff Meet M yo Clin. 33:317 1958.
41 Wallace A. G Mitchell, J H., Skinner N S J nd Sarnoff S. J Hemodynamic variables affecting the relation between mean left atrial and left entricular end-diastolic pressures, Circulation Res. 13:261 1963
42 Delman, A. J Gordon, G M Stein, E and Escher D The second sound-mitral opening snap (A2-OS) interval during exercise in the evaluation of mitral stenosis, Circulation 33:399 1966.
43 Jameson, A G P thologic ph siology in mitral valve disease. Ann New York Acad. Sc 118:486, 1965
44 Braunwald E and Frahm, C J Studies on Starling law of the heart, IV Observations on the hemodynamic functions of the left trium in man Circulation 24:633 1961
45 Fairley K F The influence of trial size and elasticit on the left atrial pressure tracing Brit Heart J 23:512, 1961
46 Hamer N A Ros S B and Dow J W Determ nants of he left trial pressure pulse in mitral al disease, Circulation 19:257 1959
47 Kjellberg, S R and Olsson, S E. Roentgenologic studies of the sphincter mechanism of the ca al and pulmonary veins, Acta radiol 41:481 1954
48 Brockman, S K D namic function of trial contraction in regulation of cardiac per formance, Am J Physiol 204:597 1963
49 Little, R C Hilton, J G and Schaeffer R. D The first heart sound in normal nd ectopic ve tricular ontractions, Circulation Res. 2:48, 1954

50. Sarnoff, S. J., Gilmore, J. P., and Mitchell, J. H.: Influence of atrial contraction and relaxation on closure of mitral valve, Circulation Res. 11:26, 1962.
51. Little, R. C.: Effect of atrial systole on ventricular pressure and closure of the A-V valves, Am. J. Physiol. 166:289, 1951.
52. Brockman, S. K.: Mechanism of the movements of the atrioventricular valves, Am. J. Cardiol. 17:682, 1966.
53. Henderson, Y., and Johnson, F. E.: Two modes of closure of the heart valves, Heart 4:69, 1912.
54. Dean, A. L., Jr.: The movements of the mitral cusps in relation to the cardiac cycle, Am. J. Physiol. 40:206, 1916.
55. Rushmer, R. F., Finlayson, B. L., and Nash, A. A.: Movements of the mitral valve, Circulation Res. 4:337, 1956.
56. Kantrowitz, A., Herwitt, E. S., and Herskovitz, A.: A cinematographic study of the function of the mitral valve in situ, S. Forum 2:204, 1951.
57. Amador, E., Thrower, W. B., and Dammin, G. J.: Dynamics of normal and diseased cardiac valves, Am. Heart J. 66:777, 1963.
58. Bond, G. S.: The relation of the auriculoventricular region to the sequence of contraction of the heart, Heart 4:1, 1912.
59. Smith, H. L., Essex, H. E., and Baldes, E. J.: A study of the movements of heart valves and of heart sounds, Ann. Int. Med. 33:1357, 1950.
60. Keith, A.: The functional anatomy of the heart, Brit. M. J. 1:361, 1918.
61. Burchell, H. B.: A clinical appraisal of atrial transport function, Lancet 1:775, 1964.
62. Skinner, N. S., Jr., Mitchell, J. H., Wallace, A. G., and Sarnoff, S. J.: Hemodynamic consequences of atrial fibrillation at constant ventricular rates, Am. J. Med. 36:342, 1964.
63. McNeish, N. A., McDermott, P. H., Rocco, A., Levin, H. S., and Booth, R. W.: Cineangiographic appraisal of mitral valve function during atrial fibrillation and premature ventricular contractions, Circulation (Suppl. 2) 32:143, 1965.
64. Friedman, B., Daily, W. M., and Wilson, R. H.: Studies on mitral valve function. Effect of acute hypervolemia, premature beats and other arrhythmias, Circulation Res. 4:33, 1956.
65. P. I, R. E. J., Oppenheimer, M. J., Lynch, P. R., and Stauffer, H. M.: Regurgitation of radiopaque contrast material through normal mitral valves in cinefluorographic studies of dogs, J. Appl. Physiol. 12:98, 1958.
66. Parker, B. M., Hudson, H. L., Smith, R. M., and Friedenberg, M. J.: Tricuspid and mitral insufficiency in normal dogs, Circulation (Suppl. 2) 32:168, 1965.
67. Daley, R., McMillan, I. K. R., and Gorlin, R.: Mitral incompetence in experimental auricular fibrillation, Lancet 2:18, 1955.
68. Bjork, V. O., Lodin, H., and Malers, E.: The evaluation of the degree of mitral insufficiency by selective left ventricular angiocardiography, Am. Heart J. 60:691, 1960.
69. Braunwald, E., Rockoff, S. D., Oldham, H. N., Jr., and Ross, J., Jr.: Effective closure of the mitral valve without atrial systole, Circulation 33:404, 1966.
70. Rushmer, R. F.: Initial phase of ventricular systole: asynchronous contraction, Am. J. Physiol. 184:188, 1956.
71. Nixon, P. G., and Polis, O.: The left atrial x descent, Brit. Heart J. 24:173, 1962.
72. Burch, G. E., Ray, C. T., and Cronvich, J. A.: Certain mechanical peculiarities of the human cardiac pump in normal and diseased states, Circulation 5:504, 1952.
73. Burch, G. E., and DePasquale, N. P.: Time course of tension in papillary muscles of the heart, J.A.M.A. 192:701, 1965.
74. Rudner, S.: Left atrial pressure curve: significance of annular ascent wing, Acta med. scandinav. 159:219, 1957.
75. Nixon, P. G. F.: Time relationship of the left atrial valve in mitral valvular disease, Brit. Heart J. 23:637, 1961.
76. Human, G. P., and Snyman, H. W.: The "V" descent of the left atrial pressure curve, Cardiologia 43:183, 1963.
77. Oriol, A., Palmer, W. H., Nakhjavan, F., and McGregor, M.: Prediction of left atrial pressure from the second sound-opening snap interval, Am. J. Cardiol. 16:184, 1965.
78. Decker, D. D., Gerbrandt, M. J., and Dean, M. I.: The exercise phonocardiogram in mitral stenosis, Am. Heart J. 71:509, 1966.
79. Julian, D., and Davies, L. G.: Heart sound and intracardiac pressures in mitral stenosis, Brit. Heart J. 19:486, 1957.
80. Nixon, P. G. F., and Wooler, G. H.: Phases of diastole in various syndromes of mitral valvular disease, Brit. Heart J. 25:393, 1963.
81. Simon, M. A., and Liu, S. F.: Calcification of the mitral valve annulus and its relation to functional valvular disturbance, Am. Heart J. 48:497, 1954.
82. Korn, D., DeSanctis, R. W., and Sell, S.: Massive calcification of the mitral annulus, New England J. Med. 26:900, 1962.
83. Hensley, S. D.: Mitral annulus calcification, Radiology 83:464, 1964.
84. Yater, W. M., and Cornell, V. H.: Heart block due to calcareous lesions of the bundle of His, Ann. Int. Med. 8:777, 1935.
85. Lev, M.: Anatomic basis for atrioventricular block, Am. J. Med. 37:742, 1964.
86. Rytand, D. A., and Lipsitch, L. S.: Clinical aspects of calcification of the mitral annulus fibrosus, Arch. Int. Med. 78:544, 1946.
87. Sheldon, W. H., and Golden, A.: Abscesses of the valve rings of the heart, a frequent but not well recognized complication of acute bacterial endocarditis, Circulation 4:1, 1951.
88. Gross, L., and Friedberg, C. K.: Lesions of the cardiac valve rings in rheumatic fever, Am. J. Path. 12:469, 1936.
89. Cruickshank, B.: Heart lesions in rheumatoid disease, J. Path. & Bact. 76:223, 1958.
90. Foster, R. W., Mitchell, ...: The anatomy and prosthetic valve design, Proc. Staff Meet. Mayo Clin. 36:582, 1961.

91. Levy, M. J. and Edwards, J. E. Anatomy of mitral insufficiency. Progr. Cardiovas. Dis. 5:119, 1962.
92. H jtmancik, M. R., Wright, J. C., Quaint, R., and Jennings, F. L. The cardiovascular manifestations of systemic lupus erythematosus, Am. Heart J. 68:119, 1964.
93. Kong, T. Q., Kellum, R. E., and Haserick, J. R. Clinical diagnosis of cardiac involvement in systemic lupus erythematosus, Circulation 26:7, 1962.
94. T ubenhaus, M., Eisenstei, B., and Pick, A. Cardiovascular manifestations of collagen diseases, Circulation 12:903, 1955.
95. Libman, E., and Sacks, B. A hitherto undescribed form of valvular and mural endocarditis, Arch. I t. Med. 33:701, 1924.
96. MacLean, N. and MacDonald, M. K. Aneurysm of the mitral valve in subacute bacterial endocarditis, Brit. Heart J. 19:550, 1957.
97. Meek, D. C., Paton, [illegible] and Blount, S. G., J. Perforation of the normal mitral valve due to staphylococcic endocarditis, Am. J. Cardiol. 17:729, 1966.
98. Saphir, O. and Leroy, E. P. True aneurysms of the mitral valve in subacute bacterial endocarditis, Am. J. P th. 24:83, 1948.
99. Blackman, S. S., J. Syphilis of the mitral valve and membranous interventricular septum of the heart, Bull. Johns Hopkins Hosp. 57:111, 1935.
100. Ludden, T. E., and Edwards, J. E. Carditis in poliomyelitis, Am. J. Path. 25:357, 1949.
101. Weinstein, L. Cardiovascular disturbances in poliomyelitis, Circulation 15:735, 1957.
102. Parmley, L. F., Manion, W. C., and Mattingly, T. W. Nonpenetrating traumatic injury of the heart, Circulation 18:371, 1958.
103. Selzsche, V. [illegible] A shrapnel splinter in the mitral valve, Ztschr. Inn. Med. 19:274, 1964.
104. Barber, H. The effect of trauma, direct and indirect, on the heart, Quart. J. Med. 13:137, 1944.
105. Creech, O. J., Ledbetter, M. K., and Reemtsma, K. Congenital mitral insufficiency with cleft posterior leaflet, Circulation 25:390, 1962.
106. Omeri, M. A., Bishop, [illegible] Oakley, C., Bentall, H. H., and Cleland, W. P. The mitral valve in endocardial cushion defects, Brit. Heart J. 27:161, 1965.
107. Wakai, C. S., and Edwards, J. E. Pathologic study of persistent common atrioventricular canal, Am. H. a. J. 56:779, 1958.
108. Rastelli, G., Kirklin, J. W., and Titus, J. L. Anatomic observations on complete form of persistent common atrioventricular canal with special reference to atrioventricular valves, Proc. Staff Meet. Mayo Clin. 41:296, 1966.
109. Ferencz, C. Atrioventricular defect of membranous septum, Bull. Johns Hopkins Hosp. 100:209, 1957.
110. Somerville, J. Clinical assessment of the function of the mitral valve in atrioventricular defects related to the anatomy, Am. H. a. t. J. 1:701, 1966.
111. Hara, M. and Cha, F. Partial cleft of septal mitral leaflet associated with trial septal defect of the secundum type, Am. J. Cardiol. 1:282, 1966.
112. Giknis, F. L. Single atrium and the Ellis-van Creveld syndrome, J. Pediat. 62:558, 1963.
113. [illegible] Kusick, V. A. Heritable disorders of connective tissue, ed. 3, St. Louis, 1966, The C. V. Mosby Company.
114. Green, G. J., Schuman, B. M., and Barron, J. Ehlers-Danlos syndrome complicated by acute hemorrhagic sigmoid diverticulitis with unusual mitral valve abnormality, Am. J. Med. 41:622, 1966.
115. Madison, W. M., Bradley, E. J., and Castillo, A. J. Ehlers-Danlos syndrome with cardiac involvement, Am. J. Cardiol. 11:689, 1963.
116. Kravetz, L. J., Lorincz, A. E., and Schiebler, G. L. Cardiovascular manifestations of the Hurler syndrome, Circulation 31:132, 1965.
117. V nace, P. W., Friedman, S. and Wagner, B. M. Mitral stenosis in an atypical case of gargoylism, Circulation [illegible]:80, 1960.
118. Crley, J. M., Lewis, K. B., Humphries, J. O. and Ross, R. S. Prolapse of the mitral valve: clinical and cineangiocardiographic findings, Brit. Heart J. 28:488, 1966.
119. Stewart, [illegible] M. A case of arachnodactyly, Arch. Dis. Child. 14:64, 1939.
120. Wunsch, C. M., Steinmetz, E. F., and Fisch, C. Marfan's syndrome and subacute bacterial endocarditis, Am. J. Cardiol. [illegible]:102, 1965.
121. Raghib, G., Jue, K. L., Anderson, R. C., and Edwards, J. E. Marfan's syndrome with mitral insufficiency, Am. J. Cardiol. 16:127, 1965.
122. Edynak, C. M. and Rawson, A. J. Ruptured aneurysms of the mitral valve in Marfan-like syndrome, Am. J. Cardiol. 11:674, 1963.
123. Read, R. C., Thal, A. P., and Wendt, V. E. Symptomatic valvular myxomatous transformation (the floppy valve syndrome), Circulation 32:897, 1965.
124. M. Kusick, V. A. Heritable disorders of connective tissue. VI. pseudoxanthoma elasticum, J. Chron. Dis. 3:263, 1956.
125. Coffman, J. D. and Sommers, S. C. Familial pseudoxanthoma elasticum and valvular heart disease, Circulation 19:242, 1959.
126. Criscitiello, M. G., Ronan, J. A., J., Besterman, E. M., and Schoenwetter, W. Cardiovascular abnormalities in osteogenesis imperfecta, Circulation 31:255, 1965.
127. Barlow, J. B. and Bosman, C. K. Aneurysmal protrusion of the posterior leaflet of the mitral valve, Am. Heart J. 71:166, 1966.
128. Gasul, B. M., Arcilla, R. A., and Lev, M. Congenital mitral regurgitation, Heart disease in children, Philadelphia and Toronto, 1966, J. B. Lippincott Company, p. 882.
129. Hewson, C. S., Blackman, M. S., Kiemenschneider, P. and Berne, A. S. Isolated congenital mitral insufficiency, J. Pediat. 64:218, 1964.
130. Br[illegible] M. F., moder tor Differential diagnosis of mitral regurgitation in childhood, Ann. I. Med. [illegible]:12 3, 1961.
131. Kesh, J. D. Congenital mitral insufficiency, Progr. Cardiovas. Dis. 5:264, 1962.

132. Carney, E. K., Braunwald, E., Roberts, W. C., Aygen, M., and Morrow, A. G.: Congenital mitral regurgitation, Am. J. Med. 33:223, 1962.
133. Talner, N. S., Stern, A. M., and Sloan, H. E.: Congenital mitral insufficiency, Circulation 23:339, 1961.
134. Levy, M. J., Varco, R. L., Lillehei, C. W., and Edwards, J. E.: Mitral insufficiency in infants, children and adolescents, J. Thoracic & Cardiovas. Surg. 45:434, 1963.
135. Jordan, J. D., and Taylor, W. T.: Case of combined congenital tricuspid and mitral insufficiency, Am. J. Dis. Child. 111:105, 1966.
136. Gilbert, G., Aerichide, N., and La Pointe, L.: Congenital mitral insufficiency associated with a ventricular septal defect, Am. Heart J. 68:107, 1964.
137. Cantez, T., D Cruz, I. A., Weinberg, M., Jr., and Fell, E. H.: Pulmonary stenosis with mitral and tricuspid incompetence, Am. J. Cardiol. 13:537, 1964.
138. Tremblay, J. P., and Simard, L. C.: Duplication of the mitral valve, Canad. M. J. 73:850, 1955.
139. Forney, W. R., Robinson, S. J., and Pascoe, D. J.: Congenital heart disease, deafness, and skeletal malformations: a new syndrome? J. Pediat. 68:14, 1966.
140. Actis-Dato, A., and Milocco, I.: Anomalous attachment of the mitral valve to the ventricular wall, Am. J. Cardiol. 17:278, 1966.
141. Bjork, V. O., Hultquist, G., and Lodin, H.: Subaortic stenosis produced by an abnormally placed anterior mitral leaflet, J. Thoracic & Cardiovas. Surg. 41:659, 1961.
142. Maiers, E., Bjork, V. O., Cullhed, I., and Lodin, H.: Transposition functionally totally corrected associated with mitral insufficiency, Am. Heart J. 59:816, 1960.
143. Elliott, L. P., Anderson, R. C., and Edwards, J. E.: The common cardiac ventricle with transposition of the great vessels, Brit. Heart J. 26:289, 1964.
144. Helmholz, H. F., Jr., Daugherty, G. W., and Edwards, J. E.: Cardiac clinics CXLV: Congenital "mitral" insufficiency in association with corrected transposition of the great vessels, Proc. Staff Meet. Mayo Clin. 31:82, 1956.
145. Dekker, A., Mehrizi, A., and Vengsarkar, A. S.: Corrected transposition of the great vessels with Ebstein malformation of the left atrioventricular valve, Circulation 31:119, 1965.
146. Rusted, I. F., Scheifley, C. H., and Edwards, J. E.: Studies of the mitral valve. II. Certain anatomic features of the mitral valve and associated structures in mitral stenosis, Circulation 14:398, 1956.
147. Weintraub, A. M., and Zvaifler, N. J.: The occurrence of valvular and myocardial disease in patients with chronic joint deformity, Am. J. Med. 35:145, 1963.
148. Bywaters, E. G. L.: The relation between heart and joint disease including "rheumatoid heart disease" and chronic post-rheumatic arthritis (type Jaccoud), Brit. Heart J. 12:101, 1950.
149. Lieberman, A.: Acute angioneurotic edema of the mitral valve, Am. Heart J. 62:714, 1961.
150. Schweizer, W., Gloor, F., Bertrab, R. von, and Aubach, U. C.: Carcinoid heart disease with left-sided lesions, Circulation 29:253, 1964.
151. Roberts, W. C., and Sjoerdsma, A.: Pathology of carcinoid heart disease, Circulation 26:717, 1962.
152. Fadell, E. J., and Denham, R. M.: Carcinoid heart disease with bilateral ventricular endocardial sclerosis, Am. J. Cardiol. 17:259, 1966.
153. Jatlow, P., and Rice, J.: Bronchial adenoma with hyperserotoninemia, biventricular valvular lesions, and osteoblastic metastases, Am. J. Clin. Path. 42:285, 1964.
154. McKusick, V. A.: Carcinoid cardiovascular disease, Bull. Johns Hopkins Hosp. 98:13, 1956.
155. V. Buchem, F. S. P., Arends, A., and Schroder, E. A.: Endocardial fibroelastosis in adolescents and adults, Brit. Heart J. 21:229, 1959.
156. Epstein, B. S.: Comparative study of valvular calcifications in rheumatic and in nonrheumatic heart disease, Arch. Int. Med. 65:279, 1940.
157. Bentivoglio, L., Uricchio, J., and Goldberg, H.: Clinical and hemodynamic features of advanced mitral regurgitation, Am. J. Med. 30:372, 1961.
158. Fertman, M. H., and Wolff, L.: Calcification of the mitral valve, Am. Heart J. 31:580, 1946.
159. Sell, S., and Scully, R. E.: Aging changes in the aortic and mitral valves, Am. J. Path. 46:345, 1965.
160. Pomerance, A.: Pathogenesis of senile nodular sclerosis of atrioventricular valves, Brit. Heart J. 28:815, 1966.
161. Eliot, R. S., Shone, J. D., Kanjuh, V. I., Ruttenberg, H. D., Carey, L. S., and Edwards, J. E.: Mitral atresia, Am. Heart J. 70:6, 1965.
162. Monroe, C. A., Maha, G. L., and Orgain, E. S.: Congenital mitral stenosis associated with coarctation of aorta, bicuspid aortic valve, hypoplasia of the left ventricle, mitral stenosis, auricular septal defect, and tricuspid valvular malformation, Am. Heart J. 55:313, 1958.
163. Noonan, J. A., and Nadas, A. S.: The hypoplastic left heart syndrome, Pediat. Clin. North America 5:1029, 1958.
164. Ferencz, C., Johnson, A. L., and Wiglesworth, F. W.: Congenital mitral stenosis, Circulation 9:161, 1954.
165. Donnally, H. H.: Congenital mitral stenosis, J. A. M. A. 82:1318, 1924.
166. Kanjuh, V. I., Eliot, R. S., and Edwards, J. E.: Coexistent mitral and aortic valvular atresia, Am. J. Cardiol. 15:611, 1965.
167. Daoud, G., Kaplan, S., Perrin, E. V., Dorst, J. P., and Edwards, F. K.: Congenital mitral stenosis, Circulation 27:185, 1963.
168. Bernstein, A., Weiss, F., and Gilbert, L.: Uncomplicated congenital mitral stenosis, Am. J. Cardiol. 2:102, 1958.
169. Gasul, B. M., Arcilla, R. A., and Lev, M.: Congenital mitral stenosis, in Heart disease in children, Philadelphia and Toronto, 1966, J. B. Lippincott Company, p. 857.

170. Singh S P Gotsman M S., Abrams, L. D Astley R Parsons, C. G. nd Roberts, K. D Congenital mitral stenosis, Brit. Heart J 29:83, 1967
171. Kahn, M Henry E. I Bruzenas, V V and Steinf ld, L. Atresia of the left trioventricular valve associated with corrected transposition of the great vessels, Am J Med 28:1013 1960.
172. Salazar E., Benavides, P Contreras, R and Espino-Vela, J Congenital mitral and tricuspid stenoses, Am. J Cardiol. 16 758, 1965.
173. Lucas, R. V J Lester R. G., Lillehei, C W and Edwards, J E. Mitral tresia with levoatriocardinal vein, Am. J Cardiol. 9:607 1962.
174. Aldridge, H. E nd Wigle, E. D Partial anomalous pulmonary enous drainage with ntact interatrial septum associated with congenital mitral stenosis, Circulation 31:579 1965
175. Braudo, J L., J vett, S N Adler D I and Kessel I Isolated congenital mitral stenosis, Circulation 15:358, 1957
176. Blumgart, L. A tumor of the mitral valve, Am. J M. Sc 134:576, 1907
177. Y ter W M. Tumors of the heart and pericardium, Arch. I t. Med. 48:627 1931
178. Wolf, E., and Vickery A. L. Primary fibrosarcoma of the heart with vertebral metastases, Arch. P th. 43:244 1947
179. Prichard, R. W Tumors of the heart, Arch Path 51:98, 1951
180. Forel, F C Two cases of primary neoplasm of the cardiac valves, Internat. Clin. 1:147 1919
181. Adamson, W W Case of primary sarcoma of the heart, J Path. & Bact. 60:344 1948.
182. Leonhardt, A. Concerning myxoma of the heart, particularly of the valves, Arch. Path Anat. u. Physiol. B 181:347 1905
183. Jacobsson, E Two cases of so-called myxofibroma of the heart valves, producing clinical symptoms and congenital vitium, An Pediat 161:1, 1943
184. Mair C. S., and Seah, C. S. Primary chondrosarcomatous mesenchymoma of the mitral valve, Thora 21:254 1966.
185. Frater R. W M and Ellis, F H J The anatomy of the canine mitral valve, J S. Res. 1:171 1961
186. Edwards, J E. The problem of mitral insufficiency caused by accessory chordae tendineae in persistent common trioventricular canal, Proc. Staff Meet. M y Clin. 33:299 1960.
187. Shone, J D Sellers, R. P Anderson R. C Adams, P J Lillehei, C. W and Edwards, J E. The developmental complex of para ch t mitral valve, supravalvular ring of left trium, subaortic stenosis, and coarctation of the aorta Am J Cardiol. 11 714 1963.
188. Rogers, H. M W ldron, B R., Murphey D F H and Edwards, J E. Supravalvular stenosing ring of left atrium in association with endocardial sclerosis (endocardial fibroelastosis) and mitral insufficiency Am. Heart J 50 777 1955.
189. Sanders, C. A., Austen, W G., Harthorne, J W Dinsmore, R. E., and Scannell, J G. Diagnosis and surgical treatment of mitral regurgitation secondary to ruptured chordae tendineae New England J Med. 276:943 1967
190. Roberts, W C. Bran wald, E., and Morrow A. G Acute severe mitral regurgitation secondary t ruptured chordae tendineae Circulation 33:58, 1966.
191. Menges, H J Ankeney J L., and Hellerstein, H. K The clinical diagnosis and surgical management of ruptured mitral chordae tendineae, Circulation 30:8 1964
192. Case records of the Massachusetts General Hospital (case 52 1966) New England J Med. 275 1244, 1966.
193. January L E., Fisher J M and Ehrenhaft, J L. Mitral insufficiency resulting from rupture of normal chordae tendineae, Circulation 26:1329 1962.
194. Frothingham C., and Hass, G M Rupture of normal chordae tendineae of the mitral valve, Am Heart J 9:492, 1934.
195. Edwards, J E., and Burchell, H. B. Endocardial and intimal lesions as possible sites of origin of murmurs, Circulation 18:946, 1958.
196. Merendino, K. A. and Hessel, E. A. The murmur on top of the head" in acquired mitral insufficiency J.A.M.A. 199:892, 1967
197. Moller J H Lucas, R. V J Adams, P J Anderson, R C., Jorgens, J and Edwards, J E. Endocardial fibroelastosis. A clinical and anatomic stud of 47 patients w th emphasis on its relationship to mitral insufficiency Circulation 30 759 1964.
198. Dinsmore, R. E Sanders, C A., and Harthorne, J W Mitral regurgitation in idiopathic hypertrophic subaortic stenosis, New England J Med. 275:1225 1966.
199. Layman, T E., and Ed ards, J E. Anomalous mitral arcade, Circulation 35:389 1967
200. Davison, S. Spontaneous rupture of papillary muscle of the heart, J Mount Sinai Hosp. 14:941 1948.
201. Smith, J C Rupture of papillary muscle of the heart report of two cases, Circulation 1 766, 1950.
202. Hope, R. B., nd Askey J M Necrosis of cardiac papillary muscle following infarction with incomplete rupture Am Heart J 44:306 1952
203. Sanders, R. J Neubuerger K. T and Ravin A Rupture of papillary muscles Occurrence of rupture of the posterior muscle in posterior myocardial infarction, Dis. Chest 31:316, 1957
204. Breneman G. M and Drake, E H. Ruptured papillary muscle following myocardial infarction with long survival, Circulation 25:862, 1962
205. Burch, G E DePasquale, N P and Phillips, J H Clinical manifestations of papillary muscle dysf nction, Arch. I t. Med. 112:112, 1963
206. Beaghler R. L., and Laurain, A. R. Rupture of cardiac papillary muscle, Arch. Path. 76:609 1963.
207. Bailas, N Functional mitral insufficiency in

acute myocardial ischemia, Am. J. Cardiol. 16:807, 1965.

208. Robinson, J. S., Stannard, M. M., and Long, M.: Ruptured papillary muscle after acute myocardial infarction, AM. HEART J. 70:233, 1965.

209. Bashour, F. A.: Mitral regurgitation following myocardial infarction. The syndrome of papillary mitral regurgitation, Dis. Chest 48:113, 1965.

210. DePasquale, N. P., and Burch, G. E.: The necropsy incidence of gross scars or acute infarction of the papillary muscles of the left ventricle, Am. J. Cardiol. 17:169, 1966.

211. Heikkila, J.: Mitral incompetence as a complication of acute myocardial infarction, Acta med. scandinav. Suppl. 475, 1967.

212. Heckel, D. B., and Kaufman, N.: Papillary muscle rupture due to myocardial abscess, Ann. Int. Med. 38:824, 1953.

213. Askey, J. M.: Spontaneous rupture of a papillary muscle of the heart, Am. J. Med. 9:528, 1950.

214. Spalding, E. D., and Von Glahn, W. C.: Syphilitic rupture of a papillary muscle of the heart, Bull. Johns Hopkins Hosp. 32:30, 1921.

215. Gomez, A. R., and Jackson, H. A.: Traumatic rupture of a papillary muscle in a child, AM. HEART J. 71:522, 1966.

216. Moller, J. H., Nakib, A., and Edwards, J. E.: Infarction of papillary muscles and mitral insufficiency associated with congenital aortic stenosis, Circulation 34:87, 1966.

217. Usman, A., Fernandez, B., Ukrebio, J. F., and Nichols, H. T.: Aberrant origin of left coronary artery combined with mitral regurgitation in an adult, Am. J. Cardiol. 8:130, 1961.

218. Burchell, H. B., and Brown, A. L., Jr.: Anomalous origin of coronary artery from pulmonary artery masquerading as mitral insufficiency, AM. HEART J. 63:388, 1962.

219. Noren, G. R., Raghib, G., Moller, J. H., Amplatz, K., Adams, P., and Edwards, J. E.: Anomalous origin of the left coronary artery from the pulmonary trunk with special reference to the occurrence of mitral insufficiency, Circulation 30:171, 1964.

220. Wiggers, C. J., and Feil, H.: The cardiodynamics of mitral insufficiency, Heart 9:149, 1922.

221. Davila, J. C.: Hemodynamics of mitral insufficiency, Am. J. Cardiol. 2:135, 1958.

222. Cohen, L. S., Mason, D. T., and Braunwald, E.: Significance of an atrial gallop sound in mitral regurgitation, Circulation 35:112, 1967.

223. Jose, A. D., Taylor, R. R., and Bernstein, L.: The influence of arterial pressure on mitral incompetence in man, J. Clin. Invest. 43:2094, 1964.

224. Braunwald, E., Welch, G. H., Jr., and Morrow, A. G.: The effects of acutely increased systemic resistance on the left atrial pressure pulse: a method for the clinical detection of mitral insufficiency, J. Clin. Invest. 37:35, 1958.

225. Schrire, V., Vogelpoel, L., Nellen, M., and Swanepoel, A.: Silent mitral incompetence, AM. HEART J. 61:723, 1961.

226. Aravanis, C.: Silent mitral insufficiency, AM. HEART J. 70:620, 1965.

Fundamentals of clinical cardiology

The second heart sound

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Careful auscultation of the second heart sound can be one of the most important and rewarding aspects of the entire cardiac physical examination. Obviously, the entire auscultatory examination should be performed with uniform care and concern. However, it is true that at times the second heart sound provides extremely important diagnostic clues. In addition, the mechanism of the variations in the second heart sound which occur in both health and disease are of considerable physiologic interest.

The purpose of the present paper is to describe the mechanism of production of the second heart sound and to discuss certain normal and abnormal variations in the second heart sound which are of diagnostic importance.

Mechanism of production of the second heart sound. During the submaximal ejection phase of ventricular systole there is a progressive decrease in right and left ventricular pressure (Fig. 1). When the pressure in the two ventricles declines below that in the great arteries, the blood in the systemic and pulmonary circuits begins to flow retrograde towards the heart, thus filling the sinuses of Valsalva. As the sinuses of Valsalva become filled, the semilunar cusps bulge towards each other to obliterate the aortic and pulmonic orifices and the retrograde flow of blood in the great arteries suddenly ceases. The impact of the column of blood in the pulmonary artery and in the aorta against the closed semilunar valves produces vibrations in the column of blood which are transmitted to the chest wall as the second heart sound.

Components of the second heart sound. For practical clinical purposes, the normal second heart sound may be considered to consist of two separate components, one component arising from closure of the aortic valve and the other from closure of the pulmonic valve. These two components may occur simultaneously or they may be separated by a variable interval in time. When there is a temporal interval between aortic and pulmonic valve closure, two distinct sounds are audible at the pulmonic area, both being relatively high pitched. If the interval between the two sounds is greater than 0.02 or 0.03 second, the ear can usually distinguish between them, a phenomenon referred to as "splitting." It is of interest that the importance of splitting of the second sound in clinical cardiac diagnosis has been generally recognized only a little over a decade.[1,2]

In the majority of normal people, the

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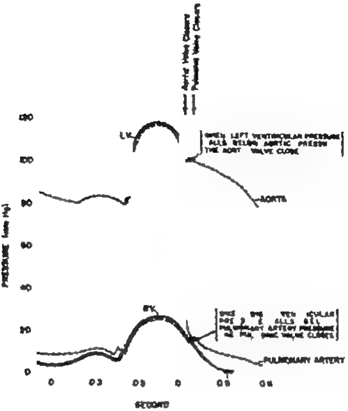

Fig. 1. Relationships of the closure of the semilunar valves to pressure changes in the left ventricle aorta right ventricle and pulmonary artery

aortic and pulmonic valves do not close precisely at the same time. Furthermore the interval between aortic and pulmonic valve closure varies continuously during the respiratory cycle. Once the temporal relationship between aortic and pulmonary valve closure is learned as well as the variations in this relationship with respiration it is possible to distinguish between that component of the second heart sound which arises from pulmonary valve closure and that component which arises from aortic valve closure.

Intensity of the second heart sound. The intensity of the second heart sound is affected by extracardiac as well as cardiac factors. Obviously *extracardiac factors* such as emphysema pericardial fluid and the thickness of the chest wall will modify the intensity of not only the second heart sound but all cardiac auscultatory phenomena. It must be appreciated that as with cardiac murmurs evaluation of the intensity of the heart sound is highly subjective.

Of the *cardiac factors* which influence the intensity of the second heart sound the most important are the anatomic position of the heart the size of the ventricles and great arteries the health of the myocardium the anatomic state of the semilunar valves and the forces exerted on the valves during closure.

It is customary to compare the intensity of the second heart sound at the aortic area with that at the pulmonic area hence the notation $A_2 > P_2$ or $P_2 > A_2$ appears in many hospital charts. However such notations are misleading because they lead to the erroneous conception that the second sound at the aortic area (A_2) is independent of the second sound at the pulmonic area (P_2). Normally the pulmonic component of the second sound is barely audible at the aortic area. However since both the aortic and pulmonic component of the second heart sound are audible at the pulmonic area it is useful to compare the intensities of these two sounds at this area. Until the age of about

20 years the pulmonic component of the second heart sound exceeds the aortic component in intensity at the pulmonic area. Between 20 and 35 years of age the two components are of essentially equal intensity. After 35 years of age the aortic component of the second heart sound exceeds the pulmonic component in intensity.

Obviously, in order to compare the intensities of the aortic and pulmonic components of the second heart sound, it is first necessary to identify the two components. This can be done easily once the temporal relationship between the two components is learned and by utilizing the variations in this relationship during deep inspiration and forced expiration.

Splitting of the second heart sound. Splitting of the second heart sound is best appreciated at or just below the pulmonic area. The pulmonic area is usually designated as the second and third intercostal space at a point approximately 2 to 3 cm to the left of the sternum. Although normal splitting is best heard at the pulmonic area, it may be audible over a wider area.

Normally, the temporal relationship between the two components of the second heart sound are such that the first component is due to closure of the aortic valve and the second component is due to closure of the pulmonic valve. The hemodynamic events underlying this relationship are graphically illustrated in Fig. 1.

During inspiration the interval between aortic and pulmonic valve closure and hence the degree of splitting increase. Therefore, during normal quiet breathing the two components of the second heart sound move apart temporally during inspiration and move together during expiration. At the end of expiration the interval between the two components of the second heart sound normally varies from no interval at all to one of about 0.03 second. When the interval between the two components is about 0.02 second the physician is usually unable to separate the two components by auscultation and a single sound is heard. During inspiration the interval between the two components may increase up to 0.06 second and the two components are readily distinguished even by a relatively untrained ear.

At least two mechanisms are responsible for the splitting of the second heart sound. First, right and left ventricular ejections are usually not synchronous. Right ventricular ejection time exceeds left ventricular time by about 0.06 second. The shorter ejection time of the left ventricle as compared to the right results in earlier closure of the aortic valve than of the pulmonic valve. The second mechanism responsible for splitting of the second heart sound is related to hemodynamic variations during respiration which are not yet completely understood. Those hemodynamic factors which are considered to contribute to splitting of the second heart sound are described in some detail below for deep inspiration and forced expiration. Briefly, the increase in the volume and duration of systemic venous return associated with *inspiration* results in an increase in the volume of right ventricular filling and, in turn, a longer time to empty the right ventricle of blood. This delays pulmonic valve closure and widens the interval between the two components of the second heart sound. On the other hand, the decrease in systemic venous return associated with *expiration* decreases the volume of blood to be ejected so that right ventricular ejection time is necessarily less, thereby hastening pulmonic valve closure and narrowing the interval between the two components of the second heart sound.

Influence of deep inspiration on the temporal relationship of the aortic and pulmonic components of the second heart sound. Deep inspiration is associated with a number of well-known hemodynamic alterations (Fig. 2) which include an increase in heart rate, a decrease in systemic arterial blood pressure, and increased splitting of the second heart sound. The change in heart rate is vagal reflex in origin. In order to understand the mechanism of the decrease in systemic arterial blood pressure and the increased splitting of the second heart sound, it is necessary to learn the physiologic consequences of deep inspiration. During quiet respiration intrathoracic pressure ranges from about −5 mm. Hg with expiration to about −9 mm. Hg with inspiration. However, during deep inspiration intrathoracic pressure may decrease to −30 or −40 mm. Hg. At the

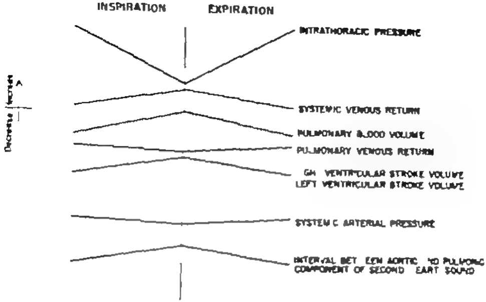

Fig. 2. Schematic representation of hemodynamic events associated with inspiration and expiration.

same time the descending diaphragm causes an increase in the intra-abdominal pressure. Deep inspiration is also associated with an increase in the tone of the small peripheral veins (capacitance vessels). Thus the over all increase in pressure gradient between the peripheral venous reservoir and the right atrium results in an increase in systemic venous return to the right side of the heart. At the same time that the increased negativity of the intrapleural pressure causes an increase in systemic venous return to the right side of the heart, it also produces an increase in pulmonary vascular capacity and pulmonary blood volume. It must be stated that the evidence for increased pulmonary blood volume during deep inspiration is inferential. Deep inspiration decreases pulmonary capillary blood volume secondary to distention of the alveoli. However, because of the decrease in intrapleural pressure during deep inspiration transmural or distending pressure of the intrathoracic veins increases. The net effect is to increase pulmonary vascular capacity and pulmonary blood volume. There is evidence that the pulmonary veins are readily distensible and are capable of functioning as a reservoir for blood. The increase in pulmonary blood volume is greater than the increase in systemic venous return with the net result that pulmonary venous return to the left atrium is decreased. Thus during deep inspiration the volume of blood ejected by the right ventricle is increased and the volume of blood ejected by the left ventricle is decreased and at the same time systemic arterial pressure declines. It is obvious that if the breath is held in deep inspiration the imbalance in the systolic discharge of the two ventricles will not be maintained. As soon as the pulmonary venous reservoir is filled, the discharge of the two ventricles will become equal. Thus, when studying the influence of deep inspiration on any hemodynamic function it is important to make the appropriate observations *during the first few beats* after beginning of deep inspiration.

The increase in right ventricular stroke volume during deep inspiration is associated with prolongation of right ventricular ejection time and delayed closure of the pulmonary valve. On the other hand, the decrease in left ventricular stroke volume during deep inspiration shortens left ventricular ejection time and hastens closure of the aortic valve. Thus, during deep inspiration the two components of the *second heart sound* move away from each other temporally, i.e., the aortic valve closes somewhat earlier and the pulmonic valve closes later than in expiration (Fig. 3). During quiet inspiration, the interval

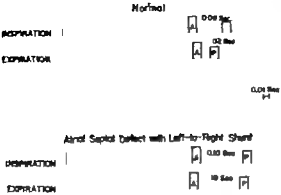

Fig. 3. Schematic representation of the relationships between the two components of the second heart sound during inspiration and expiration as observed in a normal individual and in an individual with an atrial septal defect.

between the two components of the second heart sound does not usually exceed 0.06 second, whereas in deep inspiration this interval may increase to 0.10 second.

Influence of the Valsalva maneuver on the temporal relationships of the aortic and pulmonic components of the second heart sound. The hemodynamic consequences of expiration are opposite to those of inspiration, i.e., heart rate decreases, systemic arterial blood pressure increases, and splitting of the second heart sound narrows or disappears (Fig. 2). These changes during expiration are related to the decrease in the magnitude of the negative intrathoracic pressure and in the volume of the systemic venous return. In studying the respiratory "mechanics" of the second heart sound, it is more effective to use the Valsalva maneuver to decrease negative intrapleural pressure than to use forced expiration. Indeed, although forced expiration may elevate the negative intrapleural pressure to almost zero, the Valsalva experiment will actually "raise" the intrapleural pressure to a positive value. Thus, the Valsalva maneuver will decrease venous return more effectively than will forced expiration. The elevation in intrapleural pressure results in a reduction in the pressure gradient between the right atrium and the systemic veins so that systemic venous return to the right ventricle decreases. Besides reducing systemic venous return, the Valsalva maneuver is associated with a decrease in the pulmonary venous reservoir and its capacity. In fact, the abrupt reduction in transmural pressure which occurs in the early phases of the Valsalva maneuver forces blood out of the pulmonary venous reservoir and temporarily increases pulmonary venous return to the left atrium. The decrease in right ventricular stroke volume and increase in pulmonary arterial pressure and pulmonary resistance result in early closure of the pulmonic valve, whereas the increase in left ventricular stroke volume delays closure of the aortic valve. Thus, during the Valsalva maneuver the two components of the second heart sound move towards each other, thereby even fusing into a single sound.

The hemodynamic phenomena described above and their effects on the second heart sound must be understood and constantly kept in mind to make possible a clear appreciation of the applications of this heart sound to clinical cardiology.

Clinical states associated with alterations in the second heart sound

A variety of clinical states are associated with alterations in the second heart sound.[1-4] In some instances, the nature of these alterations in the second heart sound provides highly reliable diagnostic clues. The more important clinical states which are associated with alterations in the second heart sound are described below.

Left bundle branch block. Left bundle branch block is associated with a delay in left ventricular activation and contraction, which in turn is associated with a delay in aortic valve closure. If closure of the aortic valve is sufficiently delayed, there may be a reversal in the order of semilunar valve closure, i.e., the aortic valve will close after the pulmonic valve and the aortic component of the second heart sound will follow the pulmonic component of the second heart sound. Under such circumstances, deep inspiration delays pulmonic valve closure as it does normally. Because the pulmonary valve closes before the aortic valve, inspiratory delay in pulmonic valve closure causes the pulmonary component of the second heart sound to move towards the aortic

component and thus narrow or obliterate the interval between the two components. On the other hand expiration or the Valsalva maneuver by virtue of the fact that they hasten pulmonic valve closure, causes the pulmonic component of the second heart sound to move away from the aortic component and widen the time interval between the two components of the second heart sound When deep inspiration narrows (rather than widens) and expiration or the Valsalva maneuver widens (rather than narrows) the interval between the two components of the second heart sound the phenomenon is referred to as *paradoxic splitting*.[1]

It should be obvious that it is a relatively simple matter to identify the origin of the two components of the second heart sound If *deep inspiration widens the split* between the two components, the first component must have arisen from aortic valve closure and the second from pulmonic valve closure On the other hand if deep inspiration narrows the split the first component must have arisen from pulmonic valve closure and the second from aortic valve closure Once the two components are identified it is possible to compare the intensities of the aortic and pulmonic components of the second heart sound at the pulmonic area

Paradoxic splitting of the second heart sound in left bundle branch block may be considered as *electrical* in origin being due to the delay in ventricular activation associated with left bundle branch block. Paradoxic splitting may also be hemodynamic or *mechanical* in origin due to prolongation of left ventricular ejection time such as may occur in so-called vol ume overloading of the left ventricle (e g as in patent ductus arteriosus) or left ventricular dysfunction (e g as with myocardial infarction).[12,1] Paradoxic splitting of the second heart sound may also occur in association with pressure overloading of the left ventricle. However the left ventricle tolerates pressure loads better than volume loads so that paradoxic splitting is a finding relatively late in left ventricular disease in clinical states associated with pressure overloading of the left ventricle.

Right bundle branch block Right bundle branch block is associated with a delay in right ventricular activation which in turn is associated with a delay in the onset of right ventricular ejection. Aortic valve closure is not disturbed but pulmonic valve closure is late. Thus, there is wide splitting between the two components of the second heart sound Inspiration and expiration are associated with the same variations in the relationship between the two components of the second heart sound as occur normally so that the splitting is widened or narrowed respectively

Mitral insufficiency The relationship between the two components of the second heart sound in mitral insufficiency is variable depending upon the degree and duration of insufficiency Probably early in the course of mitral insufficiency left *ventricular ejection* time is shortened resulting in early closure of the aortic valve so that the splitting is wide Under these circumstances deep inspiration results in even wider splitting of the second heart sound However in advanced left ventricular dysfunction associated with ventricular dilatation and elevated end diastolic pressure left ventricular ejection time may be prolonged The associated delay in aortic valve closure results in narrow or close splitting of the second sound

Atrial septal defect with left-to-right shunt Atrial septal defect may be associated with characteristic alterations in the second heart sound.[13,4] The left-to-right interatrial shunt diverts blood away from the left ventricle to the right ventricle so that the right ventricle receives and ejects a greater volume of blood than the left ventricle The volume overloading of the right ventricle is associated with prolongation of right ventricular ejection time On the other hand in very large atrial septal defects volume underloading of the left ventricle may result in a relatively short left ventricular ejection time Thus there is early occurrence of the aortic component but especially delayed occurrence of the pulmonic component of the second heart sound resulting in wide splitting of the second heart sound It is characteristic of atrial septal defect that deep inspiration or forced expiration produces little or no change in the interval

between the two components of the second heart sound a phenomenon referred to as "fixed splitting" (Fig 3) However in many instances of atrial septal defect and left to-right shunt, slight changes in the interval between the two components of the second heart sound do occur with respiration Fusion of the two components of the second heart sound during expiration is strong evidence against the diagnosis of atrial septal defect with left-to-right shunt.

The mechanism of "fixed splitting" of the two components of the second heart sound in atrial septal defect has been a source of debate for several years. Originally it was thought that the right ventricle which is already volume overloaded could not accept a further increase in volume during deep inspiration and thus the pulmonic component of the second sound would remain fixed Current evidence supports an interesting reciprocating mechanism whereby phasic changes in systemic venous return are counterbalanced by changes in the magnitude of the left to-right interatrial shunt. Thus, with the atria in free communication any augmentation in systemic venous return produced by inspiration is associated with a decrease in the volume of shunt flow across the atrial septal defect Since the increase in systemic venous return is more or less proportional to the decrease in shunt flow right ventricular ejection time and the time of occurrence of the pulmonic component of the second heart sound and its relationship to the aortic sound remain unchanged

Relatively fixed splitting of the second heart sound occurs in both the ostium secundum and ostium primum type defects. On the other hand small atrial septal defects (e.g sinus venosus type) with significant anomalous pulmonary venous drainage are associated with wide splitting of the second sound but the two components vary normally with respiration In such instances, free communication between the two atria and a reciprocating balance shunt and systemic venous return are not possible.

Patent ductus arteriosus Patent ductus arteriosus is associated with volume overloading of the left ventricle and a prolongation of left ventricular ejection time Aortic valve closure is delayed so that the interval between the two components of the second heart sound is narrow resulting in close splitting In the presence of a large patent ductus arteriosus, left ventricular ejection time may be so prolonged that aortic valve closure occurs after pulmonic valve closure and paradoxic splitting occurs.

Pulmonic stenosis Pulmonic stenosis results in prolongation of right ventricular ejection time, delay in pulmonic valve closure and wide splitting of the second heart sound.[8,22] The length of the interval between the two components of the second heart sound correlates fairly well with the severity of the pulmonary stenosis. The intensity of the second heart sound is usually faint in pulmonary stenosis in fact, the pulmonic component may be inaudible when the stenosis is very tight. However the correlation between the decrease in intensity of the pulmonary component of the second sound and the degree of stenosis is not as good as the correlation between the delay in the occurrence of the pulmonic component of the second sound with the degree of stenosis.

The systolic murmur associated with pulmonic stenosis m cover the aortic component of the second sound at the pulmonary area so that only the faint pulmonic component is heard (Fig 4) Under such circumstances, splitting of the second heart sound will not be detected Easily detectable wide splitting of the second heart sound at the pulmonic area usually makes the diagnosis of severe or moderately severe pulmonary stenosis unlikely because with these degrees of pulmonary stenosis the aortic component of the second heart sound at the pulmonary area would be masked

Aortic stenosis Aortic stenosis is associated with prolongation in left ventricular ejection time and a delay in aortic valve closure.[23] The aortic component of the second heart sound "moves towards" the pulmonic component resulting in close splitting of the second heart sound The average interval between the two components of the second heart sound in mid respiration is about 0 02 second in patients

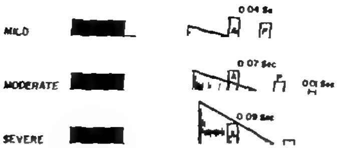

Fig. 4. The temporal and amplitude interrelationships of the murmur and the two components of the second heart sound occurring in pulmonary stenosis of various degrees of severity. Consult text.

with congenital aortic stenosis, whereas in normal subjects this interval is about 0.04 second. An interval of only 0.02 second between the aortic and pulmonic components of the second heart sound cannot usually be recognized, so that the second heart sound at the pulmonary area does not seem to be split. The prolongation of left ventricular ejection time is usually not great in patients with aortic stenosis, so that although paradoxic splitting of the second heart sound may occur, it is relatively infrequent. In fact, paradoxic splitting of the second heart sound in a patient with aortic stenosis is good evidence that the stenosis is severe.

The intensity of the aortic component of the second heart sound at the aortic area may be normal, decreased, or increased in aortic stenosis. When the aortic component is increased in intensity, the sound may be louder at the apex than at the aortic area. The intensity of the aortic component of the second heart sound is probably not a reliable means of differentiating between aortic (valvular) stenosis and subaortic stenosis.

Pulmonary stenosis with ventricular septal defect (tetralogy of Fallot). Tetralogy of Fallot is now considered in terms of the two primary defects, i.e., pulmonary stenosis and ventricular septal defect. Depending upon the relative severity of the two defects, a wide hemodynamic and clinical spectrum is possible, ranging from a large right-to-left shunt at rest to absence of a right-to-left shunt either at rest or upon exercise but a large left-to-right shunt. Obviously, within this hemodynamic spectrum there will also be a wide auscultatory spectrum. It has been taught for many years that the second heart sound in tetralogy of Fallot is pure, arising exclusively from aortic valve closure, and that the second sound remains single on inspiration and expiration. In a phonocardiographic analysis of the second heart sound of 63 patients with tetralogy of Fallot, the pulmonic component of the second heart sound was not evident in 6 patients with extreme tetralogy and 18 patients with severe tetralogy of Fallot. On the other hand, in 3 of 17 patients with moderate tetralogy and 18 of 21 patients with mild tetralogy of Fallot, the pulmonic component of the second sound could be demonstrated. It should be pointed out that the pulmonic component of the second heart sound is not always heard best at the so-called pulmonic area. In clinical examination of patients, the pulmonic component of the second heart sound can only be demonstrated at the third or fourth left intercostal space. Thus, it is possible to demonstrate the pulmonic component of the second heart sound phonocardiographically in some patients with tetralogy of Fallot, but the sound is almost always too faint to be audible during clinical auscultation. However, the demonstration of the pulmonic component of the second heart sound phonocardiographically may be of practical value. Theoretically, because the right and left ventricles are in communication through a ventricular septal defect, the pressures and ejection times of the right and left ventricles are identical, i.e., the two ventricles function as a single chamber. However, because of the pulmonary stenosis, the aortic left ventricular pressure gradient reverses before the pulmonic right ventricular pres-

sure gradient so that aortic valve closure precedes pulmonic valve closure by a longer interval than normal Since the two chambers are in free communication one would expect little respiratory variation between the components of the second heart sound The interval between the two components of the second heart sound in tetralogy of Fallot usually ranges between 0 06 and 0 12 second. It is probable that this splitting is due to the delayed reversal of the pulmonic-right ventricular pressure gradient associated with the pulmonary stenosis. Indeed one would anticipate that the severity of the anatomic defects may be reflected by the characteristics of the second heart sound i.e. the more severe the pulmonary stenosis the wider the interval between the two components of the second heart sound and the larger the ventricular septal defect the greater the degree of fixation of these components during inspiration.

There is a need to correlate the phonocardiographic findings with hemodynamic and postmortem data. The varied auscultatory picture in tetralogy of Fallot serves to emphasize the fact that this congenital cardiac defect presents a wide spectrum of clinical hemodynamic and anatomic possibilities and that clinical reports must clearly define the relative severity of the various defects comprising the tetralogy of Fallot to be meaningful

Isolated ventricular septal defect In isolated ventricular septal defect the second heart sound usually varies in a normal fashion with respiration i.e. the interval between the two components of the second heart sound widens with inspiration and narrows with expiration.[37,38] However in large ventricular septal defects, right ventricular ejection time may be prolonged and left ventricular ejection time shortened so that there is abnormally wide splitting of the two components of the second heart sound The splitting however is not fixed

Idiopathic dilatation of the pulmonary artery The pulmonic component of the second heart sound may be greatly accentuated in intensity and be more ringing in quality in patients with idiopathic dilatation of the pulmonary artery The interval between the aortic and pulmonic components of the second heart sound varies normally with respiration. The accentuation of the pulmonic component of the second heart sound is probably due to proximity of the dilated pulmonary artery to the chest wall as well as to the possibility that the dilated pulmonary artery serves as a sounding chamber for the pulmonic component of the second heart sound.

Constrictive pericarditis An unusual type of splitting has been noted in patients with constrictive pericarditis in which deep inspiration is associated with an abrupt but transient increase in the interval between the aortic and pulmonic components of the second heart sound The change in the time interval will last for only one or two heartbeats so that the physician must auscultate particularly carefully The splitting is due almost entirely to early closure of the aortic valve with little or no change in the time of closure of the pulmonic valve.

Mitral stenosis In mitral stenosis, because of fibrotic thickening of the various elements of the mitral valve apparatus and because of altered mechanics of the mitral valve, opening of the valve is associated with an audible sound referred to as an opening snap The opening snap may be audible at the pulmonic area in which case it may be misinterpreted as a widely split second heart sound. However careful auscultation particularly during deep inspiration will permit identification of both components of the second heart sound which occur before the opening snap is heard. When in doubt it may be helpful to determine the relationship between the sounds at the pulmonic area following exercise or with the assumption of the supine position with the legs raised These maneuvers are associated with an increase in blood flow and relatively greater prolongation of right ventricular ejection than of left ventricular ejection time, resulting in widening of the interval between the aortic and pulmonic components of the second heart sound However in the presence of mitral stenosis increased blood flow results in an increase in left atrial pressure which, in turn is associated with early opening of the mitral valve and early occurrence of the opening snap.

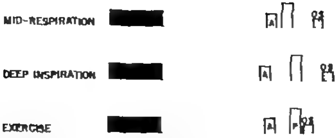

Fig 5 The influences of respiration and exercise on the two components of the second heart sound and the opening snap occurring in mitral stenosis. Consult text.

Because the opening snap occurs after the pulmonic component of the second heart sound the delay in pulmonic valve closure and the hastening of mitral valve opening associated with increased blood flow causes the two sounds (pulmonic component of the second sound and opening snap) associated with these events to move towards each other Thus, in a patient with mitral stenosis and split heart sounds at the pulmonary area exercise will widen the interval between the aortic and pulmonic components of the second heart sound but will narrow the interval between the pulmonic component of the second heart sound and the opening snap (Fig 5)

It should be mentioned that mitral stenosis is usually associated with some degree of pulmonary hypertension and as is discussed below chronic pulmonary hypertension is associated with close rather than wide splitting of the second heart sound at the pulmonary area Thus the mere presence of a wide splitting at the pulmonary area in a patient with mitral stenosis should lead one to suspect that the second component of the split sound is an opening snap rather than the pulmonic component of the second heart sound or that the pulmonary arterial blood pressure is not elevated very much and the mitral stenosis is relatively mild.

The so-called 2-OS interval' i e the time from the onset of the second heart sound (aortic component) to the onset of the opening snap has been carefully studied particularly in its relationship to the hemodynamic severity of the underlying mitral stenosis[27] It should be clear that following aortic valve closure the pressure in the left ventricle must decrease below that in the left atrium before the mitral valve can open and produce a snap. This requires a certain interval of time which is easily measured on the phonocardiogram and may be estimated during routine clinical auscultation It is obvious that the higher the left atrial pressure the sooner the ventricular pressure will decrease below it and thus the shorter the 2-OS interval This interval usually varies from about 0 05 second in very tight mitral stenosis up to 0 11 second in the less severe cases.

Pulmonary hypertension The elevated pulmonary artery pressure in pulmonary hypertension results in early reversal of the pressure gradient between the right ventricle and pulmonary artery so that the pulmonic valve closes early and with increased intensity This occurs in spite of the fact that pulmonary hypertension would be expected to delay right ventricular ejection time Therefore the interval between the aortic and pulmonic components of the second heart sound is narrow i e there is close splitting Deep inspiration produces only slight widening of the splitting Since the pulmonary valve closes against high pressure the pulmonic component of the second heart sound is accentuated

When pulmonary hypertension develops in a patient with atrial septal defect wide fixed splitting of the second heart sound characteristic of uncomplicated atrial septal defect may be replaced by closer splitting of the second heart sound with a somewhat high pitched and accentuated pulmonic component characteristic of pulmonary hypertension

Although the second heart sound i

closely split in chronic pulmonary hypertension, it may be widely split in acute pulmonary hypertension such as pulmonary embolism. Reasons for these differences are not entirely clear.

Systemic hypertension. The temporal relationships between the aortic and pulmonic components of the second heart sound are usually normal even in severe arterial hypertension. However, in a small percentage of patients with arterial hypertension, prolongation of left ventricular ejection time may delay aortic valve closure so that the second heart sound at the pulmonic area is either closely split or single. Occasionally, ventricular ejection time may be so prolonged that aortic valve closure occurs after pulmonic valve closure and paradoxic splitting of the second heart sound occurs.[13]

The aortic component of the second heart sound is accentuated in arterial hypertension. It may also have a peculiar tambour-like quality (bruit de tabourika of Potain) which is quite characteristic. The tambour-to-ringing" quality of the second heart sound may persist for some time after arterial blood pressure decreases. This is an important finding because an aortic component of the second heart sound which is tambour in quality in a patient with normal arterial blood pressure should prompt the examiner to seek an explanation for the absence of an elevated arterial blood pressure, such as a myocardial infarction or a dilatation of the root of the aorta and sinuses of Valsalva as encountered with luetic aortitis or other diseases of the aorta.

Congestive heart failure. The temporal relationships between the aortic and pulmonic components of the second heart sound vary according to the relative efficiency of the two ventricles as pumps. Theoretically, in pure *right ventricular failure*, prolongation of right ventricular ejection time results in a delay in pulmonic valve closure so that the second sound at the pulmonic area is widely split. However, in severe failure the ventricle can increase its stroke output very little if at all, so that deep inspiration results in little or no change in the interval between the aortic and pulmonic components of the second heart sound. It would be expected that the more severe the failure in contractile function the greater the degree of fixing between the two components of the second heart sound.

In pure *left ventricular failure*, prolongation of left ventricular ejection time results in delayed aortic valve closure and narrowing of the interval between the aortic and pulmonic components of the second heart sound. During inspiration the interval between aortic and pulmonic valve closure widens. However, aortic valve closure may occur after pulmonic valve closure in left ventricular failure, so that inspiration results in narrowing rather than widening of the interval between the two components of the second heart sound (paradoxic splitting).[13]

In *biventricular failure*, the ventricular ejection time of both ventricles is prolonged, so that the effect of prolonged ventricular ejection on the time of valve closure tends to "balance out" and normal splitting occurs. However, because of the impaired ability of the right ventricle to increase its stroke output, the interval between the two components of the second heart sound either remains unchanged with deep inspiration or narrows slightly, depending upon the capacity of the pulmonary vascular bed and relative contractile capacities of the two ventricles.

Arrhythmias. The second heart sound does not undergo any characteristic changes in most of the arrhythmias.

In complete atrioventricular dissociation, the second heart sound may be accentuated, but it is the first heart sound that is of diagnostic importance in this conduction defect (bruit de canon). Depending upon the relative timing of atrial and ventricular systole, the atrial sound may occur just before or after the second heart sound, giving the impression that the second heart sound is split—a phenomenon referred to as pseudosplitting. The inconstancy of the interval of split easily differentiates pseudosplitting from true splitting of the second heart sound.

The second heart sound associated with an atrial or ventricular premature beat may be diminished or even absent, depending upon the amount of diastolic filling which occurred during the shortened diastolic period preceding the premature

beat. Because of asynchronous closure of the semilunar valves due to alterations in the sequence of conduction, the second heart sound associated with a ventricular premature beat may vary widely depending upon the origin of the premature beat. For example, when the ectopic focus is in the left ventricle, the second heart sound is usually widely split with a normal A_2–P_2 sequence. On the other hand, when the ectopic focus is in the right ventricle, paradoxic splitting of the second heart sound (P_2–A_2) usually occurs.

The intensities of the heart sounds including the second sound vary in association with premature beats and other disturbances in cardiac rhythm. For example, during the compensatory pause the ventricles fill markedly, and therefore the first beat after the premature beat is a vigorous one and all sounds are particularly loud. This and other variations in heart sounds associated with disorders of the heartbeat are too extensive and complex to warrant consideration in this presentation. Furthermore, these alterations are of little clinical diagnostic value.

Influence of pharmacologic agents on the second heart sound

Studies on the influence of pharmacologic agents on auscultatory cardiac phenomena have been primarily concerned with changes in the duration and intensity of murmurs brought about by various drugs.[26-30] Little attention has been paid to the influence of drugs on the second heart sound. These considerations can be extensive; therefore, the effect of pharmacologic agents on the second heart sound is only briefly discussed below.

Drugs which lower systemic peripheral vascular resistance. Drugs which lower systemic peripheral vascular resistance (e.g., amyl nitrite) decrease mean aortic pressure and shorten left ventricular ejection time. Therefore, such drugs increase the interval between the two components of the second heart sound, i.e., they widen splitting at the pulmonary area. Because of the decrease in aortic pressure, the intensity of the second heart sound at the aortic area is diminished.

Drugs which increase systemic peripheral vascular resistance. Drugs which increase peripheral vascular resistance (e.g., metaraminol) increase mean aortic pressure and prolong left ventricular ejection time. The interval between the two components of the second heart sound is narrow, i.e., there is close splitting, and the aortic component of the second heart sound is increased in intensity.

Summary

The second heart sound can provide important diagnostic information. Although the entire auscultatory examination should be performed with equal care, close attention to the second heart sound may be particularly rewarding. The fact that the interval between the two components of the second heart sound, the intensity of the aortic and pulmonic components of the second heart sound, and/or the relationship between the two components of the second heart sound during the phases of respiration correlate with the severity of the anatomic and hemodynamic disturbances in many pathologic states is of great value to the clinician.

REFERENCES

1. Leatham, A., and Towers, M.: Splitting of the second heart sound in health, Brit. Heart J. 13:575, 1951.
2. Leatham, A.: Splitting of the first and second heart sound, Lancet 2:607, 1954.
3. Van Der Hauwaert, L. G.: The effect of the Valsalva maneuver on the splitting of the second sound, Acta cardiol. 19:518, 1964.
4. Wolferth, C. C., and Margolies, A.: Asynchronism in contraction of the ventricles in the so-called common type of bundle-branch block; its bearing on the determination of the side of the significant lesion and on the mechanism of split first and second heart sounds, Am. Heart J. 10:425, 1935.
5. Aygen, M. M., and Bra...ald, E.: The splitting of the second heart sound in normal subjects and in patients with congenital heart disease, Circulation 25:328, 1962.
6. Beck, W., Schrire, V., and Vogelpoel, L.: Splitting of the second heart sound in constrictive pericarditis with observations on the mechanism of pulsus paradoxus, Am. Heart J. 64:765, 1962.
7. Schrire, V., and Vogelpoel, L.: The role of the dilated pulmonary artery in abnormal splitting of the second heart sound, Am. Heart J. 63:501, 1962.
8. Leatham, A.: The second heart sound. Key to auscultation of the heart, Acta cardiol. 19:395, 1964.
9. De Leon, A. C., Jr., Perloff, J. K., T..., H., and M...: The ... right bock

drome Clinical cardiovascular manifestations, Circulation 32 193, 1965.

10. Burch G E., and Phillips, J H Selected clues in cardiac auscultation, Am. Heart J 63 1 1962

11. Gray I R. Paradoxical splitting of the second heart sound, Brit. Heart J 18:21 1956.

12. Dickerson, R. B., and Nelson, W P Paradoxical splitting of the second heart sound An informati clinical notation Am. Heart J 67:410 1964

13. Abbott, J A., and Whipple G. H Paradoxic splitting of the second heart sound in y temic hypertension. The role of myocardial competence Dis. Chest 46:404 1964

14. Yurchak P M and Gorlin R. Paradoxical splitting of the second heart sound in coronary heart disease, New England J Med 269 741 1963.

15. Leatham, A., and Gray I Auscultatory and phonocardiographic signs of trial septal defect, Brit. Heart J 18 193, 1956.

16. Dimond, E. G and Benchimol A Phonocardiography in trial septal defect Correlation between hemodynamics and phonocardiographic findings, Am Heart J 58:343 1959

17. Hoffman A., Morgan, J J Good m, J F and Fields, H. Auscultatory nd phonocardiographic findings in septal defect. A study of 93 surgically treated patients, Circulation 28:94 1963

18. Barritt D W Davies, D H., nd Jacob G. Heart sounds nd pressures in trial septal defect, Brit Heart J 27:90, 1965

19. Leatham A and Weitzman D Auscultatory and phonocardiographic signs of pulmonary stenosis, Brit Heart J 19:303 1957

20. Dimond, E G and Benchimol, A. Phonocardiography in pulmonary stenosis Special correlation bet een hemodynamics nd phonocardiographic findings, Ann Int. Med 52:145 1960.

21. Vogelpoel, L and Schrire V Auscultatory and phonocardiographic assessment of pulmonary tenosis with intact ventricular septum, Circulation 22:55 1960

22. Gamboa, R., Hugenholtz, P G., nd Nadas, A S Accuracy of the phonocardiogram in assessing severity of ortic nd pulmonary tenosis, Circulation 30:35, 1964

23. Braunwald, E., Goldblatt, A Aygen, M M Rockoff S. D nd Morrow A. G Congenital aortic stenosis. I Clinical and hemodynamic findings in 100 patien s, Circulation 2 :426, 1963

24. Vogelpoel L. and Schrire, V Auscultatory and phonocardiographic assessment of Fallot tetralogy Circulation 22 73, 1960.

25. Macieira-Coelho, E., and Coelho, E. Auscultatory and phonocardiographic diagnosis of Fallot-type complex, Cardiologia 41:193 1962.

26. Burch, G. E DePasquale, N P and Phillips, J H Tetralogy of Fallot associated with well developed left ventricular muscle mass and increased lif span, Am. J Med. 36:54 1964

27. Van Der H waert, L., and Nadas, A. S. Auscultatory findings in patients with small ventricular septal defect, Circulation 23:886, 1961

28. Leatham, A nd Segal, B. Auscultatory and phonocardiographic signs of ventricular septal defect th left-to-right sh t, Circulation 25:318, 1962.

29. Proctor M H Walker R. P Hancock, E. W and Abelmann, W H. The phonocardiogram in mitral valvular disease. A correlation of Q-I and 2-OS intervals with findings t catheterization of the left side of the heart and at mitral valvuloplasty Am. J Med 24:861 1958.

30. Vogelpoel, L Nellen, M Swanepoel, A., and Schrire V The use of amyl itrite in the diagnosis of systolic murmurs, Lancet 2:810, 1959

31. Vogelpoel, L Schrire V Nellen, M and Swanepoel, A The use of amyl nitrite in the differentiation of Fallot tetralogy and pulmonary stenosis with intact ventricular septum, Am Hear J 57:803 1959

32. Beck, W Schrire V Vogelpoel, L Nellen, M and Swanepoel, A Hemodynamic effect of amyl itrite and phenylephrine on the normal h man circulation and their relation t changes in ardiac m rmurs, Am J Cardiol 8:341 1961

33. Bourvaros, G A Effect of norepinephrine on the phonocardiographic auscultatory nd hemodynamic fea ures of congenital and acquired heart disease Am J Cardiol 8:328, 1961

34. Schrire, V Vogelpoel, L Beck, W Nellen M and Swanepoel, A The effects of amyl nitrite and phenylephrine on he intracardiac murmurs of small ventricular septal defects, Am Heart J 62:225 1961

35. Endrys, J and Bartova, A Pharmacological methods in the phonocardiographic diagnosis of regurgitan murmurs, Brit Heart J 24:207 196_

Surgical treatment of valvular heart disease

Part IV Mitral valve surgery. A brief for closed valvuloplasty and repair in preference to prosthetic replacement

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A reappraisal of mitral valve surgery must consider 2 major unresolved controversies. The first is the dispute as to whether closed or open mitral valvuloplasty (commissurotomy) is preferable for mitral stenosis. The second question is whether open mitral repair with annuloplasty is preferable to prosthetic replacement of the mitral valve for regurgitation and mixed lesions (stenosis and insufficiency). There is little comparative data available. We prefer mitral annuloplasty to valve replacement in patients with mitral insufficiency and closed repair of the mitral valve for mitral stenosis when possible. The conclusions are based upon experience with over 400 mitral valve operations.

Closed valvuloplasty versus open repair for mitral stenosis. Experience with closed mitral valvuloplasty has been good and follow-up data reveal that good early results have been sustained for up to 13 years. Careful documentation of the anatomic and dynamic features of the valve by line drawings and written descriptions at the time of the operation permit certain retrospective conclusions. An effective valvuloplasty requires (1) good opening of the valve orifice, (2) mobilization of the major leaflet by separation of the chordae where fused, (3) little or no calcification in the valves, and (4) little or no insufficiency present or created at the time of the operation. Reoperation has been required primarily for 2 reasons. Either inadequate opening and mobilization of the valve was achieved initially, or the presence or creation of significant insufficiency was a feature of the first operation. Restenosis has been rare; in a few patients progression of the disease with calcification occurred as a late phenomenon. There was no correlation between age and the probability of successful closed valvuloplasty.

At present, all operations for mitral stenosis are performed with the pump oxygenator assembled and on a standby basis. If the preoperative assessment suggests isolated mitral stenosis with no insufficiency by auscultation or cardiac catheterization and little or no radiological evidence of calcification, the possibility of a closed operation is anticipated. If the valve cannot be well opened and mobilized or if significant insufficiency is found or produced by the manipulation, the opera-

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tion is then performed by the open technique. It is imperative to assess the result under dynamic conditions. Frequently the systemic pressure must be raised with pressors to normal or higher levels to appreciate the magnitude of regurgitation. Hypotension or a low cardiac output may give the erroneous impression of a satisfactory result.

In summary, closed mitral valvuloplasty has resulted in sustained good results for up to 13 years. There have been no operative deaths at this center in the past 7 years. With careful surgical technique it is often unnecessary to replace blood loss by transfusion, so the risk of hepatitis is minimized. There are no follow-up data of comparable duration for open repair and no evidence that open repair will be superior when rigid criteria for closed valvuloplasty are followed.

Open repair versus prosthetic replacement for mitral stenosis (or stenosis and insufficiency). Our approach has been to repair, not replace the mitral valve whenever possible. Replacement is done when calcification prevents adequate opening and mobilization of the valve or when there is severe shrinkage and fibrosis of the valve substance. Despite the variety of mitral valve prostheses available, all have serious drawbacks. At this time, patients with prosthetic valves need continuous anticoagulation. Despite maintenance of a satisfactory prothrombin time, the incidence of thromboembolism is appreciable. Bleeding complications are not uncommon, including hemorrhage into the gastrointestinal tract, pleura, pericardium, cranium, and other less vital areas. Other complications exclusive to prosthetic valves include endocardial fibrosis found at autopsy, interference with left ventricular function caused by the cage of ball valves, absorption of lipid by the silastic ball, and significant leakage at the suture line.

Open repair of the mitral valve is dependent upon a reliable method for the correction of mitral regurgitation. Asymmetric measure annuloplasty provides this technique and will be discussed in detail below. In repairing the mitral valve because of stenosis or mixed lesions, the major leaflet of the valve must be well mobilized and fall away during diastole so that little resistance to flow through the mitral orifice remains. Frequently it is necessary to deliberately produce insufficiency in order to accomplish this. Portions of the minor leaflet may be excised and discarded, particularly if heavy calcification is present. Papillary muscle and chordae must be separated. Correction of the regurgitation is then achieved by a modified measured asymmetric annuloplasty. It is rarely necessary to plicate the free edge of the valve because of ruptured chordae or to advance the major leaflet by inserting a gusset of pericardium.

The operative mortality rate is approximately 5 per cent. Follow-up studies for up to 6 years reveal a 2 per cent incidence of thromboembolism and a similar incidence of infection. Initial good results have been sustained for up to 6 years.

Annuloplasty versus prosthetic replacement for mitral regurgitation. There are few advocates of repair of the regurgitant mitral valve and prosthetic replacement is generally the rule. In our opinion the preference for replacement is not based upon objective data, a perfect prosthesis has not yet been developed and the mitral valve should be repaired whenever possible. Indeed, except for marked calcification and rarely because of severe fibrosis, it has not been necessary to replace a valve because of mitral regurgitation. Repair by asymmetric measured annuloplasty has been applied to isolated mitral regurgitation in more than 80 patients. The patients in this series ranged in age from 3 to 63 years. In all of them mitral regurgitation was the only lesion requiring repair. The pathology included rheumatic valvulitis, with stretching and loss of valve substance, ruptured chordae and perforation of the leaflets secondary to subacute bacterial endocarditis, and ruptured chordae from both papillary muscles without obvious etiology. A total of 11 children were operated upon despite the hazard of recurrent rheumatic activity. These patients all had severe congestive failure. Eighty per cent of the patients have had good to excellent results for up to 7 years. In 15 per cent of the patients, despite a significant systolic murmur, there has been good clinical improvement and reoperation has not been considered

In 5 per cent of the patients, reoperation has been necessary or is planned. In one patient valve replacement was required because of extensive destruction secondary to infection which followed annuloplasty. There have been no deaths in the past 70 operations. In most patients, clinical improvement has been associated with a marked reduction in cardiac size although this has not been universal. Although anticoagulation had not been used postoperatively, there has been only one embolic complication. All patients have resumed regular activities and occupations. Eight babies have been born to this postoperative group with no difficulties during pregnancy. One patient, now 7 years since her operation, has had 2 uncomplicated pregnancies. Long term efficacy is exemplified by this patient in whom marked reduction in cardiac size, absence of murmur, and symptomatic improvement has been sustained.

The concept of hemodynamic predictability. The minimal mitral valve orifice area permitting flow without a gradient can be predicted by use of hydraulic formulae derived by Gorlin. From this cross-sectional area, the circumference may be calculated and then measured precisely. Sutures are placed asymmetrically by measurement to create an orifice of predetermined size based upon the patient's cardiac output requirements. The asymmetrical placement of annulus sutures permits utilization of the commodious and relatively undistorted central portion of the major leaflet as the mobile component of the repair. Sutures are placed only in the annulus and do not immobilize the leaflets or close the commissures. Deliberate constriction of the annulus is inherent in the technique and assures the competency of the repair. Iatrogenic stenosis does not result when repair is based upon measurement.

REFERENCES

1. Ankeney, J. L.: Indications for closed or open heart surgery for mitral stenosis, Ann Thoracic Surg 3:389, 1967.
2. Morrow, A. G., Oldham, H. M., Elkins, R. C., and Braunwald, E.: Prosthetic replacement of the mitral valve, Circulation 35:962, 1967.
3. Reed, G. E., Tice, D. A., and Clauss, R. H.: Asymmetric exaggerated mitral annuloplasty. Repair of mitral insufficiency with hemodynamic predictability, J Thorac & Cardiovas Surg 49:752, 1965.

Annotations

Chronic intestinal ischemia

In 1936 Dunphy[2] noted that acute infarction of the midgut due to superior mesenteric thrombosis was preceded by prodromal symptoms in approximately 50 per cent of the cases. These symptoms of abdominal angina, which are due to stenosis or occlusion of the visceral arteries, form a well-recognized clinical entity, but only in recent years has it been possible to correct this by appropriate surgical procedures.

In 1965 Dardik and his co-workers[1] collected accounts of only 18 cases successfully treated surgically (including cases reported by Morris and his colleagues), but since then Morris and his colleagues have reported 31 cases treated surgically and Rob has reported 33 cases. This small number of cases, most of which were treated in large centers, suggests that the condition is rare or that its recognition is difficult.

The principal difficulty in diagnosis is lack of awareness on the part of the physician, who fails to include intestinal ischemia in his differential diagnosis when a patient presents with typical abdominal pain. Persistent abdominal pain and loss of weight are constant features of the condition, but Fry and Kraft[3] emphasize that the over-all symptom pattern is not stereotyped.

Watt and associates emphasize that the condition is to be differentiated from suspected carcinoma of the alimentary tract, atypical duodenal ulcer, and certain causes of the malabsorption syndrome. Patients with abdominal pain and loss of weight suggestive of carcinoma, in whom barium investigations have proved negative, should be suspected of having chronic intestinal ischemia, especially if there is other evidence of atherosclerosis. Doubtful radiological reports of duodenal ulcer in patients whose symptoms of ulcer are not typical and in whom weight loss is an important feature should also give rise to suspicion of intestinal ischemia and the diagnosis clarified by other means.

Malabsorption is common in visceral ischemia and probably occurs much more frequently than the 26 per cent incidence reported by Heard and his co-workers[4] in a collected series. Watt and his colleagues found evidence of steatorrhea, abnormal jejunal histology, diminished intestinal disaccharidase activity, and impaired Bromsulphalein excretion in some of their cases. In the light of this experience, chronic intestinal ischemia must be added to the list of causes of malabsorption.

Increased experience now shows that chronic intestinal ischemia may be due to one of two causes: (1) atherosclerosis involving the visceral arteries and producing stenosis or occlusion of one or more of the three principal visceral arteries and (2) stenosis of the celiac axis alone.

During 1966 to 1967 several authors[5] reported cases in which celiac axis stenosis was caused by extrinsic pressure due to fibrous bands, adhesions, or diaphragmatic pressure. The age group of these patients is less than that of the atherosclerotic group and the etiology is obscure. The onset of symptoms in adult life suggests the possibility of an acquired alteration in the relationship between the proximal abdominal aorta and the diaphragm leading to the celiac axis appearing to take origin from the aorta behind the median arcuate ligament of the diaphragm. Division of the constricting structures appears to afford relief of symptoms.

There is likely to be an increase in the number of cases of intestinal ischemia diagnosed at the stage where surgery is possible, but the long-term results of operation are not yet available. In atherosclerosis this is dependent on the state of the cerebral and coronary vessels as well as the intestinal arteries, but, in nonatherosclerotic celiac axis stenosis, the prognosis would seem to be good.

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REFERENCES

1. Dardik, H., Seidenberg, B., Parker, J. G., and Hurwitt, E. S.: Intestinal angina with malabsorption treated by elective revascularization, J.A.M.A. 194:1206, 1965.
2. Dunphy, J. E.: Abdominal pain of vascular origin, Am. J. M. Sc. 192:109, 1936.
3. Fry, W. J., and Kraft, R. O.: Visceral angina, Surg. Gynec. & Obst. 117:417, 1963.
4. Heard, G., Jefferies, J. D., and Peters, D. K.: Chronic intestinal ischaemia. Successful aorta/superior mesenteric bypass, Lancet 2:975, 1963.
5. Marable, S. A., Molnar, W., and Beman, F. M.

Abdominal pain secondary to coeliac axis compression, Am J Surg 111:493, 1966
6. Morris, G C J Crawford, E. S., Cooley D A and De Bakey M E Revascularization of the coeliac and superior mesenteric arteries, Arch Surg 81:95 1962
7. Morris, G. C., J De Bakey M E. and Bernhard, M A Abdominal angina, Surg Clin. North America 46:919 1966.
8. Rob C. G. Surgical disease of the celiac and mesenteric arteries Arch Surg 93:21 1966.
9. Watt, J Kennedy W tson, W C., nd Haase S. Chronic intestinal Ischaemia, Brit. M J 3 199 1967

The effect of clofibrate on platelets

A number of studies ha how that Atromid or Atromid-S influence platelet function. I particular it has been demonstrated that platelet dhesiveness is decreased in some subjects by administration of these drugs Studies of platelet survival ha show that patients receiving these compounds have prolongation of platelet survival and diminished platelet t rnover in comparison to control subjects The activ material ppears to be lofibrate itself and not lofibr te plus androsterone The relevance of these observ tions t the problem of thrombosis associated with ascular diseases is still not clear However experience with another set of compounds with pparently similar actions suggest that there may be an important effect It has been observed that anti-inflammatory and related drugs also prolong platelet survival in man nd experimental animals. *This prolongation of plat let surv al and reduction of plat let t rnover has been show t* be associated with inh bition of the teraction of platelets with surface timuli such collagen. It has been show experimentally tha these drugs have a significant effect on experimental thrombosis and the formation of platelet aggregates response t essel injury *It may w ll be therefore* that in dd tion t the effect on serum lipid he effect of lofibrat on platelet f nction will lso be important n the management of vascular d seases

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Gas endarterectomy

I recent ears tandard open disobliteratn endarterectomy for therama of vessel situated below the inguinal ligament ha largely been superseded by bypass procedures The main reason for this has been an nacceptably high incidence of post operativ thrombos ssociated w th the former method, largely due t the leng h of the suture line and the irregular lumen Although more success achieved when combi ed with the sertion of long ein grafts the operating tim is onsiderably increased except in localized block.

There are many exc llent reports of the es It of saphenous ein bypass operat n but the alterna ive use of prosthetic graft in this uation has not proved sufficientl uccessful in most hand

It ould seem th t there is till place for femoropopliteal endarterectomy if the method ed ca be dapted to a oid the dra back of the es tabli hed echniques Thi particularl so hen it is remembered that there are between 10 nd 25 per cent of patient whom the saphenous ei is nsuitable f r se

To this end several designs of strippers ha been dev loped ttempt t perform blind learance w thou t the necessity f opening the entire artery I our experienc these are unsatisfactory because of the considerable prac ical dif ficulty in obtai ing mooth d veet m plane f the high risk, both of rupt ring the wall and le ing tags behind ith consequent hrombosis A further disadvantage the " now plow effect, hereby branches tend t be bl ked by t ers of therama hich are pushed the rm

It th became lear th t there need f r dissecting agent which wo ld accura ely f the separation plane nd at the same tim en f r the orif es of branches to be le red Trial

nd other fluids injected under pressure into the arterial all emulating the hydraulic mechanism of dissecting aneurysm were found unsatisfactory[17] as the vessel wall tended to become soggy and edematous. Despite this, such procedure has apparently been used with success in this country.[18]

In August 1966, Sobel and associates[19] published a paper entitled "Gas endarterectomy" in which they described their initial experience using carbon dioxide as a dissecting agent. At the London Hospital we have now performed 16 operations utilizing this technique and published a preliminary report on the first ten cases in 1967.[20]

Following the application of proximal and distal limiting clamps, carbon dioxide is injected into the vessel wall through a 24/26 gauge needle. When the gas enters the dissection plane the adventitia is lifted off the inelastic atheromatous core and a gas wave of separation passes almost instantaneously along the vessel. By multiple needle insertions along the length of the vessel exposed, almost complete separation is ensured. There is considerable variation in the distance travelled by the gas in individual cases. For the femoropopliteal artery full exposure is not usually necessary but it has been found to be advantageous also to dissect in the region of the adductor hiatus as most difficulty is encountered here and it enables the artery to be gassed directly at this site. The dissection plane follows naturally into the branches and the atheromatous cuff surrounding the mouths is separated. Provided there is the usual fairly sharp return to normal undiseased vessel wall beyond the origin of the branch, a sharp division without flap formation can generally be obtained. This is largely dependent on the fact that the gas will not dissect healthy arterial wall.

After gassing, short arteriotomy is made at either end and the central core is usually found hanging loose in the lumen at these points. To ensure complete freedom throughout the length of the artery a long curved spatula through which CO_2 is flowing is now passed along the dissection plane. This rides on a cushion of gas and effectively separates points of persistent adhesion. Occasionally a separate arteriotomy is required at a particularly stubborn area as under no circumstances, of course, should force be used. The core can now be withdrawn and the arteriotomies closed with distal tacking sutures to prevent flap valve formation if necessary.

The high solubility of carbon dioxide appears to eliminate the risk of embolus while the possibility of rupturing the vessel wall at the pressures employed (preneedle pressures up to 300 mm. Hg) is avoided by the fact that any excess gas can readily escape through the porous outer wall. The effectiveness of branch clearance is demonstrated by the frequent excellent "backflow" obtained from the clamped vessel while the uniform dissection plane is readily confirmed by the study of postoperative arteriograms.

The procedure requires considerable practice and like Sawyer, train... carried out extensive postmortem trials before progressing to clinical application. Persistent trouble is still encountered in removing the core which is often of such irregular

Table I

Number of operations	16
Indication for operation	
Intermittent claudication	11
Rest pain	3
Pregangrene	2
Operation	
Iliofemoral clearance	4
Femoropopliteal clearance	12

Table II. Postoperative complications

None	10
Transient edema of leg	4
Thrombosis	1*
Hemorrhage	1†

*Thrombosed after 6 hours. Re-explored and following removal of proximal tag and thrombectomy the distal pulses remain palpable 3 months later.

†Due to rupture of vein patch on the popliteal artery. Re-sutured with restoration of pulses.

size that portions are even larger than the proximal lumen of the vessel through which it has to be withdrawn. We are experimenting with various different instruments to try and overcome this problem.

Table I shows the indications for operation and the operations performed in our first 16 cases. All remain patent to date, but of course with a follow-up period of between 9 to 1 month only, no conclusions can be drawn. However the early results appear promising. These cases were treated by gas endarterectomy alone and I have excluded all those in which the method was used in combination with any other vascular procedure.

Of particular interest is the application to coronary arteries. In postmortem studies[21] we have shown that it is possible to clear considerable lengths of these vessels and we have been able to remove 8 cm. of core from both the right and left coronary arteries, and at the same time reopen numerous branches. Although there are many problems in translating this to clinical use, involving particularly the selection of cases and maintenance of adequate myocardial circulation during the clearance, there seems no reason why they should not be overcome. Indeed Sawyer has now had the opportunity of operating on a few such patients with some encouraging early results in right coronary occlusions.[22,23]

In conclusion, it appears that the method of carbon dioxide gas endarterectomy may prove a useful surgical procedure with certain advantages over other presently available methods.

Since submission of this annotation, the follow-up now ranges from 12 to 4 months, and to date all

vessels remain patent. A further 15 femoropopliteal procedures ha'e ow been carried out

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The gas spatulas and ancillary equipment as used in this work can now be obtained from Becton, Dickinson & Company Rutherford, N J

REFERENCES

1 Dos Sa tos, J C Presse med. 57:544 1949
2 Edwards, W S. Composit reconstruction of small leg arteries after endarterectomy Surgery 51:58, 1962
3 Webster J H. Open femoro-popl teal endarterectomy with long vein patch, Brit J Surg 53:607 1966.
4 Baddeley R. M Lawson L. J Ashton, F and Slaney G E aluation of togenous vei bypass grafts for femoro-popliteal arterial occlusion, Brit. M J 2:410, 1967
5 Linton R. R and Darling R. C A togenous saphenous vein bypass grafts in femoro-popliteal obliterative arterial disease Surgery 51:62, 1962.
6 DeWeese, J A. Barner H B. Mahoney E B nd Rob, C G A togenou vei bypass grafts and thromboendarterectomies for therosclerotic lesions of the femoro-popl teal arteries, Ann. Surg 163:205 1966.
7 Szilagyi, D E Sm th, R F and Elliot, J P Venous tografts in femoro-popliteal arterioplasty Observations in the treatment of oc lusive disease Arch Surg 89 113 1964
8. Dale W A A togenous vei grafts for femoro-popl teal occlusion, J A M A. 196:494 1966
9 Gutel k, J R Kremdler S and Loke, J C Comparative evaluation of togenous vein bypass graft and endarterectom in superficial femoral artery reconstruction Surgery 57:28, 1965
10. Ashton F Slaney G and Raine A G H Femoro-popliteal arterial obstructions Late results of teflon prostheses and arterial homografts, Brit M J 2:1149 1962
11 Cockett, F B nd Maurice B A. Evolution of direct arterial surgery for claudication and ischaemia of legs, Brit. M J 1:353 1963
12. Dale, W A Pridgen W R. and Shoulders, H H Failure of composit grafting in small human arteries, Surgery 51:258, 1962
13 Edwards, W S Lat occlusion of femoral and popl teal fabric arterial grafts, Surg Gynec. & Obst. 110 714 1960.
14 Irvine W T Kenyon, J E nd Stiles, J J Early results i 95 patient undergoing femoro-popl teal bypass graft, Brit. M J 1:360, 1963
15 Shaw R S Reconstructive vascular surgery New England J Med. 266:339 1962
16. Szilagyi, D E Pfeifer J R and DeRusso, F J Long term evaluation of plastic arterial substitutes an experimental stud Surgery 55 165 1964
17 Taylor G W Arterial grafting for gangrene, An Roy Coll Surg Eng 31 168, 1962.
18. Cannon, J A. Barker W F and Kawakami, I G. Femoral-popl teal endarterectom in the treatment of obliterative therosclerotic disease Surgery 43 76, 1958
19 Kaplitt M J Personal comm ication and T ylor R S. U published work
20. Tibbs, J T Letter Lancet 2:613 1967
21 Sobel, S. Kapl tt M J Reingold M and Sawyer P N Gas endarterectom Surgery 59:517 1966.
22 T ylor R S. Ga endarterectom Lancet 2:281 1967
23 T ylor R S Unpublished result
24 Sawyer P N Kaplitt, M J Sobel, S and DiMaio, D Application of ga endarterectomy to therosclerotic peripheral vessels nd coronary arteries, Circulation (Suppl I) 35 163, 1967
25 Sawyer P N Personal comm t

What death is like

By irtue of its uniformity universality and inevitability de th is perhaps the most normal of all physiological tates Yet, little is know about the ubjectiv responses which occur during the process of dying i man. T he sure death nd the dying process have been f orit subject of my tical writers but their writing consist of little more tha preconceived notions and philosophical tt tudes toward dying I addi tion, the psychiatric literature bounds with descript ons of ma reactions t and ttitudes toward the idea f death, he concept of d th. However informat on about p hic reactions during de th is me ger The troduction of effectiv method f cardiac resusc t tion h made possible some interesting insigh t the nature of de th in man and has placed the physician in the unique position of being able t explore the associated psychic experiences ith dying and de th Thus by questioning patient who ha been successf lly resuscitated after the heart ha stopped

long enough for consciousness to be lost for three or four minutes, it is possible to gain some idea of what dying is like. We have done this on a number of occasions and have found that the psychic reactions during dying were remarkably similar among all patients questioned.

At the onset of cardiac arrest most patients experienced a pleasant feeling as though they were entering a peaceful sleep. There was no fear or anxiety. They became unconscious and were completely unaware of the activities around them. If resuscitation procedures had not been undertaken all would have ended in an eternal sleep after the initial pleasant beginning. However, with resuscitation before serious cerebral damage had occurred, consciousness was regained after variable periods of time. At this time many patients felt pleasant again and were pleased to know they were still alive.

None of the patients questioned so far has recalled any unpleasant experience while unconscious or while entering this state. To them it was like deep sleep and if their hearts had not been started again this sleep would have been eternal.

It may be argued that these patients were not dead. This would, of course, introduce problems in defining death. Nevertheless, if their hearts had not been restarted they would have merely continued into the eternal state of unconsciousness and degenerative processes which had been in progress for a few minutes would continue until the individual had entirely perished.

In the patients under consideration death is viewed as a *continuum which effectively begins* when the circulation stops and progresses until no life processes are active in any cell of the body. Obviously, because of the early deterioration of the brain, *any psychic experience must be limited to the earliest few minutes of this process*. Thus if one considers death as a continuum or as a process, then certainly these patients who have been resuscitated after several minutes of absent heart action have experienced and retrieved psychic information from as deep within this continuum as is possible. Since return of consciousness is probably not possible after arrest of the cerebral circulation for more than 4 or 5 minutes, then all potential for recall and communication of any psychic experiences are eliminated after this period of time.

Investigations into the nature of the boundless number of changes accompanying the process of death have been relatively meager. A fertile field for gaining new insights into the processes of life (the absence of death) would appear to lie here, and further studies are certainly indicated. It is possible to study by objective methods (e.g., chemically) the functions of any organ in the body during the process of death, and in many, evidence of activity will extend deep into the continuum. Since at the present time psychic experience cannot be relegated to objective terms, the interview method becomes the only tool for their expression. This was the tool used in the present investigation of the very earliest phase of the process of death in man.

As crude as the tool utilized in this study seems to be, and thus the data so obtained, there seems to be no better model presently available to study the natural process of death than the victim of prolonged cardiac arrest who then experiences successful resuscitation. Certainly any mental experience with the process of death must come from the memory of the individual involved.

Regardless of one's definition of death, in our present society cardiac arrest and resuscitation are viewed by most patients and their families as death and return to life. It is within this context, at least, that man's psychic experience with this "death" should hold particular importance for all physicians. From this investigation it appears that "biologic death" is not an unpleasant experience. *To man it is only a deep eternal sleep.*

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Book reviews

NEW TRENDS IN BASIC LYMPHOLOGY. By J. M. Collette, G. Ja tet, and E. Schoffeniels. Basel und Stuttgart, 1967. Birkhauser Verlag. 255 pages.

These proceedings of a symposium on lymphology held in Charleroi, Belgium, on J ly 11 to 13, 1966 should interest those who did not ttend nd those who do not follow the literature on lymphatics closely. As w th most symposia these days, several papers are presented each followed by a discussion. Th reader w ll find the discussion more interesting than the papers, especially those discussions in which members of the group seem t question the data nd conclusions presented by the respecti e speakers. A total of 17 papers are presented and the subjects discussed 'ary a great deal. The session nd the published report follow the well-established proced re of the well-know Ciba Symposia. This book should be of value to anyone stud ing the lymphatics.

VASCULAR HISTOCHEMISTRY. By C. W. M. Adams. Chicago, 1967. Year Book Medical Publishers. 448 pages. Price $22.50.

Professor Adams pathologist t Guy's Hospital Medical School in London, has written rather unusual and mu h-needed book. Histopathology of blood essels has certainly been neglected the past. This book rev als mportant additional nformation that can be derived from histopathology. Although the book would be of interest t pathologist primarily it should interest all linicians, especially those studying nd managing ascular diseases. The book is well written nd well 'llustrated nd the bibliography is quit extensive. This monograph is highly recommended to pathologists physicians, and n estigators engaged in the study and treatment of ascula diseases.

CIRCULATION IN THE EXTREMITIES. By David I. Abramson, M.D. New York and London, 1967. Academic Press Inc. 557 pages. Price $22.50.

This book by Doctor Abramson is w ll written and well illustrated. The problems discussed are among the most important in clinical medicine. Doctor Abramson ha devoted most of his t tention t the peripheral circulation and his own cont ibution ha been mport t. This book presents the methods used in measurement of blood flow. Both the simple and more complex ones re discussed. Each chapter has good bibliography. This is good book which I recommended t all linicians who are interested in peripheral ascular disease. It hould be of particular value to those who tre t peripher l sc lar disease and those interested i the function of diseased essels.

ATHEROSCLEROTIC VASCULAR DISEASE. Ed ted by Albert N. Brest, M.D. and John H. Moyer, M.D. New York, 1967. Meredith Publishing Company. 534 pages. Price $17.50.

This monograph consists of the proceedings of the sixteenth Hahnemann Symposium held in Philadelphia. There were many contributors nd many phases of the problem of atherosclerosis were discussed. Among the contributors ere pathologists, epidemiologists, biochemists, physiologists, cardiologists, and surgeons. Those who follow the literature on atherosclerosis fairly well will find little if anything new. This monograph which conforms to the t ndard of the previous ones, serves as a single sour and review of data on this subject. The bibliographies are good and the papers ell ritten and illustrated.

ACID-BASE PHYSIOLOGY IN MEDICINE—A Self Instruction Program. By Robert W. Winters, M.D., Knud Engel, Mag. Sc., and Ralph B. Dell, M.D. Westlake, Ohio, 1967. The London Company. 290 pages. Price $3.85.

This book is a self-study presentation on linical problems in cid-base balance. The authors describe various chemical, biochemical, physiological, and linical aspects of acid-base balance that should interest the clinician. The material is in the form of preliminary fundamental statements followed by questions. The reader studies the statements answers the questions, and then ncovers the answers to check on himself. The book is ell organized nd thoughtf lly presented to self-educat the reader. Simple, clear and sef l diagrams and illustrations are presented. Anyone who studies this book caref lly especially if he nderstands the reasons for the disturbances in acid-base balance in the clinical states discussed will ha e profited great deal from his effort nd so will his patient. The appendix includes method of analysis and useful nomograms which are welcome feat res of the b k.

DEEP TH OMBOPHLEBITIS, Pathology and Tre t ment. By J. Alex Haller, J. M.D. Volume VI in the series M jor problems in l ical surgery. J. Engelbert Dunphy, M.D. Consulting editor. Philadelphia and London, 1967. W. B. Sa nders Company. 130 pages. Price $5.75.

This monograph of 130 pages represents a brief discussion of an important subject i medicine hich concerns surgical and nonsurgical physi cians and special'sts. I spite of increa ng interest in thromb embolic phenomena the disease cont nues essent ally nabated and age of ma y

deaths toda Doctor Haller eight chapters include discussions of evidence, clinical syndrome, venography pathophysiology complications historical development of treatment, and surgical management.

The book is well written and illustrated but is really review of much reviewed and discussed problems. As would be expected, the views of Doctor Haller prevail For example, he included very little from Fagan extensive experiences nor does he ttempt to evaluate them for the less informed reader The figure page 69 fails to consider the effect of gravitational forces on the arterial side of the circulation. The pressures illustrated would indicat that blood flow backward in the feet when man is standing The presentation of hemodynamic phenomena, therefore, is extremely limited and inadequate. This may be due i large part to the brevity of presentatio of complex subject. This monograph would be of interest primarily to surgeons who wish to know Doctor Haller opinions on deep thrombophlebitis This is usef l and clearly written book.

THE CONTRACTILE PROCESS. Proceedings of symposium sponsored by the New York Heart Association Boston, 1967 Little, Brow & Company 299 pages Price $7.00.

This is the proceedings of the symposium on the contractile process held in New York City This important subject is summarized by several papers on the following subjects. (1) the contractile processes in macromolecules (2) contractile processes in striated muscle, (3) comparative aspects of muscle contraction, and (4) contractile processes in nonmuscular systems. Each paper is followed by an interesting discussion nd good bibliography The papers are very interesting and the discussions even more interesting This publication makes it possible for the reader t profit from this important symposium and to study the data and arguments critically The book is highly recommended not only to physiologists but also to cardiologists.

THE YEAR BOOK OF CARDIOVASCULAR AND RENAL DISEASES (1966 to 1967 Year Book Series) By Eugene Braunwald, M D W Proctor Harvey M D John W Kirklin, M D Alexander S Nadas, M D Oglesby Paul, M D Victor E. Pollak, M.D Robert W Wilkins, M D and Irving S. Wright, M D Chicago, 1967 Year Book Medical Publishers, 480 pages. Price $10.50

This 1966 to 1967 abstract of selected papers published on cardiovascular and renal diseases conforms to the format of the previous reviews. The reader should remember the abstracts were selected from the hundreds of papers published in this field and, therefore, do not constitute a complete survey of the literature for that period. This 1966 to 1967 series should help the busy physician leisurely to survey many papers, even though they are selected ones This continues to be a usef l publication.

Books received

COLLECTED WORKS ON RHEUMATIC FEVER. By Leo M Tara New York, 1967 I ternational Professional Publication, Inc., 276 pages.

IF YOUR HUSBAND HAS CORONARY HEART DISEASE. By Robert III Sonneborn, New York, 1968 Hearthstone Book, Carlton Press, 69 pages. Price $2.00

MEDIUM CH IN T UBERCULOSIS. Edited by John R. Senior Transactions of Special Symposium held t the Annenberg School of Communications, University of Pennsylvania, March 9 and 10 1967 Philadelphia, 1968, Universi y of Pennsylvania Press, 100 pages

MODERN TREATMENT January 1968, Vol 5 N 1 1 TREATMENT OF CONGENITAL HEMORRHAGIC DISORDERS Edited by Oscar D Ratnoff 2 TREATMENT OF DISORDERS OF GROWTH AND DEVELOPMENT Ed ted b Roberto F Escamilla

Announcements

The American Institute of Ultrasonics in Medicine will hold its annual meeting on Nov. 6 to 9, 1968, in the Monteleone Hotel, New Orleans, La. The first day of the meeting will be devoted to tutorial papers on the basic principles of diagnostic ultrasound and a workshop session on applications in echoencephalography, cardiology, ophthalmology, obstetrics, gynecology, abdominal investigations, and Doppler studies. The last day will be devoted to terminology on diagnostic ultrasound to be adopted by the AIUM and on methods to measure the performance of the equipment.

Scientific papers are invited on clinical applications and developments in technique and in instrumentation. A half-page abstract, including figures, should be sent by Sept. 15 to C. Kossoff, *Biophysical Research Laboratory, University of Illinois, Urbana, Ill.* These will be published as proceedings of the meeting. The registration fee is $25.00.

The Fourth International Congress on Hyperbaric Medicine will be held at the Park Hotel, Sapporo (the city for the 1972 Winter Olympic Games), Japan, on Sept. 2 to 4, 1969.

A Five Day Congress in Cardiology will be held in Mexico, Oct. 29 through Nov. 2, 1968, the week after the Olympic Games. The faculty will be composed of Abdo Bisteni, M.D., Mexico; P. G. F. Nixon, M.R.C.P., London; Joseph K. Perloff, M.D., Washington; and Jose Ponce de Leon, M.D., Mexico. The directors will be Demetrio Sodi-Pallares, M.D., Mexico, and Henry J. L. Marriott, St. Petersburg. For further details, write to the Rogers Heart Foundation, 500 First Federal Building, St. Petersburg, Fla.

The American Academy of Allergy will hold its twenty-fifth annual meeting at the Americana Hotel, Bal Harbour, Fla., on March 15 to 19, 1969. Additional information is available from the Executive Office, 56 N. Milwaukee St., Milwaukee, Wis. 53202.

The Sixth World Congress of Cardiology will be held in London, England, on Sept. 7 to 12, 1970. Details can be obtained from the Chairman of the Organizing Committee, in care of Conference Services, Ltd., 11 Whitehall Court, London S.W. 1, England.

A Course in Modern Concepts of Radiological Special Procedures Techniques and Room Design will be given on Oct. 18, 19, and 20, 1968, at the *Mallinckrodt Institute of Radiology*, Washington University School of Medicine, St. Louis, Mo. This course will offer up-to-date information on room design and the selection of x-ray and accessory equipment necessary to perform modern radiologic special procedures. For information, contact David O. Davis, M.D., or Ruben Kuchler, M.D., Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S. Kingshighway, St. Louis, Mo. 63110.

American Heart Journal

October 1968 Volume 76 Number 4

Editorial

The value of the angiotensin infusion test in the diagnosis of true renovascular hypertension

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At the 1964 Meeting of the American Society for Clinical Investigation, Kaplan proposed the angiotensin infusion test as diagnostic of true renovascular hypertension. This test consisted of the infusion of an angiotensin solution (0.2 μg per milliliter of 5 per cent glucose in water) at a rate sufficient to obtain a rise of 20 mm. Hg in diastolic blood pressure or until a rate of 20 μg of angiotensin per kilogram body weight per minute was reached. The rate of infusion (nanogram per kilogram body weight per minute) was reported high in all cases of renovascular hypertension in contrast with other hypertensive states (essential, renal, parenchymatous hypertension, and primary aldosteronism) with the exception of malignant hypertension. The results were clear-cut and the test appeared of distinct value.

Although it is based on the assumption that the resistance to the pressor effect of exogenous angiotensin was presumably due to already high levels of endogenous angiotensin, no satisfactory explanation was given for the fact that the normal subjects had a response to exogenous angiotensin similar to that shown by the patients with renovascular hypertension.

Not many months went by before the specificity of the test as a diagnostic procedure for true renovascular hypertension was seriously questioned, if not rejected. Veyrat emphasized the importance of the sodium balance in the pressor response to angiotensin, a point already made by Kaplan and Silah but probably not sufficiently emphasized. Other workers found high resistance to the pressor effect of exogenous angiotensin in a number of hypertensive patients with renal parenchymatous diseases and in others receiving natriuretic agents. There was also a good deal of confusion in the designation of patients with true renovascular hypertension as separate from those with hypertension associated with renal artery stenosis. In many patients studied, no indication of cure or failure of surgery was given with at least one year's observation. This makes one doubt whether these patients truly had renovascular hypertension. Finally, two deaths during angiotensin infusions were reported, one in Paris and a second in New York. One of these two deaths was due to a ruptured cerebral aneurysm. This serves to emphasize the definite risk imposed upon patients by the angiotensin infusion, especially when the preinfusion

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diastolic pressure is above 110 to 115 mm Hg.

Since this test was based on the assumption that the decreased pressor responsiveness to exogenous angiotensin in patients with true renovascular hypertension was due to increased levels of endogenous angiotensin, a study was made by Silah and associates[3] to confirm this assumption. Previously in 1965 Genest and co-workers have emphasized the importance of high plasma renin activity levels, of a systolic pressure gradient beyond the stenosis greater than 30 mm. Hg, and the absence of arteriolar changes in the involved kidney as important criteria for the diagnosis of true renovascular hypertension. These studies, emphasizing the importance of plasma renin activity determinations, have since been confirmed by several groups. Using these criteria, Silah and associates have studied *three groups of hypertensive* patients: (1) those with essential hypertension, (2) those with essential hypertension associated with renal arterial obstruction, and (3) those with true renovascular hypertension (presenting the above criteria and cured by operation). Each patient had been thoroughly studied for plasma electrolytes, renal function, and renal *angiography. The mean pressor dose of* angiotensin infusion in the patients in Group 3 was 9.8 ng. per kilogram per minute in contrast to 3.8 in those in Groups 1 and 2. The correlation between the pressor dose of infused angiotensin and the patients' renin activity levels was significant ($p < 0.01$). The authors emphasized that if the test is to be meaningful, strict attention must be given to obtaining a stable basal blood pressure, to the regulation of sodium intake at 120 to 150 mEq. per day, by insuring normal blood volume by prior infusion of at least 250 ml. of normal saline, by withholding natriuretic drugs, and demonstrating the absence of significant parenchymatous renal diseases. With these reservations, the angiotensin infusion test has a certain value as an adjunct diagnostic tool for true renovascular hypertension.

However, one should always remember the risk involved to the patient's life in attempting to raise by 20 mm. Hg a basal diastolic blood pressure that is already above 110 to 115 mm. Hg! It is our opinion that the test cannot replace the direct measurement of plasma renin activity and that as soon as this measure*ment becomes available in more labora*tories, the angiotensin infusion test will have outlived its usefulness.

REFERENCES

1. Veyrat, R., *Brunner, H. R., Manning, E. L.*, and Müller, A. F.: Confrontation de l'action pressive de l'angiotensine des taux de la rénine plasmatique, et de l'aldostéronurie chez l'homme. Intern. Club on Arterial Hypertension, First Meeting, Paris, 1966, L'Expansion Scient. Fr. Editors, p. 259.
2. Kaplan, N. M., and Silah, J. G.: The effect of angiotensin II on the blood pressure in humans with hypertensive disease, J. Clin. Invest. 43:659, 1964.
3. Silah, J. G., Strong, C. G., Nowaczynski, W., and Genest, J.: The angiotensin infusion test and peripheral venous renin activity, Canad. M. A. J. 96:1397, 1967.

Clinical communications

Ventricular synchronous and demand pacing

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Doris J. W. Escher, M.D.
Bronx, N. Y.

Successful clinical application of cardiac pacing techniques by means of pacers asynchronous with cardiac action and insensitive to spontaneous cardiac activity led to the development of "triggered" units responsive to cardiac activity, the atrial synchronous cardiac pacemaker[1] and subsequently demand (standby) pacemakers.[2] The first responds to physiologic and pathologic atrial activity, while the latter reacts to normal (conducted or spontaneous) or aberrant ventricular activity (Table I).

Two varieties of noncompetitive pacemakers exist and operate in different fashions, though both are electrically related to atrial synchronous pacing. The first demand (standby) circuit, called *stimulus blocking*,* is set to emit impulses at intervals of 860 msec. (70 impulses per minute) on a regular asynchronous basis. The stimulating electrode is the sensor of electrical activity. A QRS complex of intraventricular field between 2 and 35 mv. (with an amplifier band width of 4 to 200 cycles) blocks the timing circuit which provides for the next pacer stimulus and initiates a recycle. However, 400 msec. must have elapsed from the preceding pacer stimulus or spontaneous contraction and the intraventricular QRS complex must reach the required intensity. A ventricular complex less than 400 msec. from the preceding ventricular contraction will not block the next pacer impulse as it will fall into the refractory period of the pacer sensor. The function of this variety of pacemaker has been described elsewhere.[2-4]

The second, the ventricular *synchronous pacemaker*,† is at all times synchronized to

Table I. Pathologic rhythms corrected by pacing

Rhythms	No. of patients
Regular sinus rhythm to complete heart	34
block.	1
Nodal rhythm to complete heart block	3
Sinoatrial arrest	
Second degree heart block with bradycardia	8
Drug induced heart block	6
Total	52

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*Ventricor II-Cordis Corporation, Miami, Fla.
†Ectocor-Cordis Corporation, Miami, Fla.

the R wave of ventricular contraction and no delay occurs between sensing of the QRS complex and emission of the stimulating impulse (Fig 1) In the presence of spontaneous ventricular activity the pacemaker impulse continually falls into the absolute refractory period of ventricular contraction and no response is produced at normal or rapid ventricular rates. However should the spontaneous ventricular rate fall below 70 electrical contractions per minute the pacemaker will revert to the intrinsic asynchronous, automatic rate with which all synchronous units are provided (Fig 2) This unit is functional at all times and therefore provides an underlying pacemaker rhythm for the reduction of multifocal ventricular contractions. A 400 msec. refractory period follows each pacemaker emission whether at the automatic pacemaker rate or in response to a spontaneous ventricular contraction An early ventricular contraction within that period will not block the next pacemaker impulse

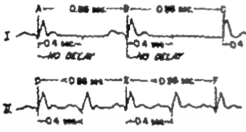

Fig 1 This diagram of the mode of function of the ventricular synchronous pacer indicates the lack of delay between spontaneous ventricular activity and the synchronized pacemaker emission. The escape interval of the pacemaker is 0.86 sec In the absence of spontaneous cardiac contractions (*A* and *B*), both of which show superimposed pacer artifacts, a paced complex (*C*) appears at the escape interval The pacemaker refractory period of 0.4 sec is indicated after each pacemaker impulse. The lower diagram is of conducted rate sufficiently rapid that each QRS complex falls within the pacemaker refractory period. Pacemakers response is one half the conducted rate (*D* *E*, and *F*).

In the presence of a functioning ventricular synchronous pacemaker with right bundle branch block development of the intraventricular signal occurs earlier within the left ventricle than the right, and the limb lead electrocardiogram (ECG) shows this QRS complex well before it is sensed by the right ventricular lead. The pacer artifact is then superimposed on the limb lead QRS complex well beyond its onset This should not be interpreted as a malfunction of the unit (Fig 3)

The ventricular synchronous pacemaker follows the ventricular rate down to its automatic level of 70 beats per minute and up to the maximum synchronous rate of 125 beats per minute as does the conventional atrial synchronous pacemaker With a consistent spontaneous ventricular rate below 70 beats per minute the automatic pacer rate is dominant Above 125 spontaneous beats per minute the pacer is refractory to each succeeding beat producing a 2 1 block in pacer response (Fig 4)

It is difficult to know the duration of battery life of either of these units as they have not been clinically available long enough to justify estimates. As the ventricular synchronous pacer emits an impulse with each ventricular contraction spontaneous or pacemaker induced it is possible for the actual emission rate to be well in excess of 70 impulses per minute The best estimate therefore is that this pacemaker will function for about the same period of time as the atrial synchronous pacemaker or about 18 to 24 months. The stimulus

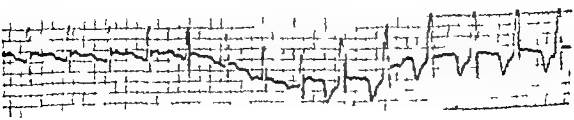

Fig 2 The complexes to the left are all pacemaker induced the cardiac rate is lower than the pacemaker automatic rate As the conducted rate becomes more rapid, spontaneous complexes appear with superimposed pacer artifacts (right).

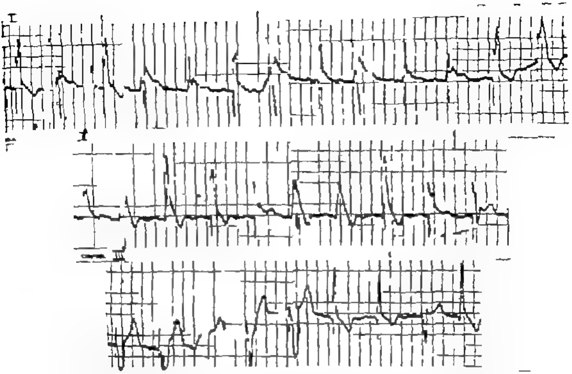

Fig. 3. During spontaneous ventricular activity with right bundle branch block, long delay exists between onset of the QRS complex and the pacer artifact. This results from the late development of a right intraventricular field sufficiently intense to cause pacer emission. I the pacer nduced and fusion complexes, the pacer artifact precedes the rest of the QRS complex. Those complexes resulting from A-V conduction show the late presence of the pacer artifact.

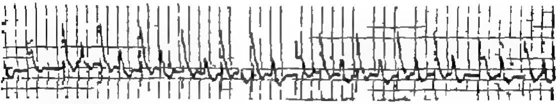

Fig. 4. I the presence of ventricular tachycardia above 125 beats per minute the pacer is refractory to alter nat complexes yielding 2:1 cardiac to pacemaker rate.

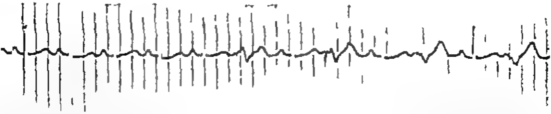

Fig. 5. Determination of threshold of cardiac response, in the presence of sinus rhythm is accomplished by coupled pacing synchronized to the preceding spontaneous QRS complex. The conducted rh thm on the left has entricular complexes t intervals of 725 msec. The introduction of pacer artifact (sixth complex from the left) at interval of 600 msec produces ventricular complex and leaves the heart refractory for the next conducted complex. This alternation continues ithout competition as long as the pacer impulse is at or above threshold. As the impulse falls below threshold normal A-V conduction returns.

blocking pacemaker will probably be operative for a greater period though perhaps still shorter than an asynchronous, fixed rate pacemaker partially because the sensing circuit itself consumes energy

Determination of threshold of ventricular response to electrical stimulation during placement of a demand (standby) pacemaker while the patient is in sinus rhythm is as important as during complete block.[4] The technique is that of synchronization of a pacer to a spontaneous QRS complex with a synchronized delay as long as 600 msec before the pacemaker impulse. With appropriate timing the pacer produced complex will precede the next spontaneous complex which will then not occur as the heart is refractory Such coupled pacing continues while the tested output is reduced until ventricular capture is lost and sinus rhythm returns (Fig 5)

Indications for demand (standby) pacing

Varying A V conduction The most frequent indication for demand (standby) pacing is varying A V conduction sinus rhythm to complete heart block with asystole or ventricular tachyarrhythmia. The pacemaker lies dormant (stimulus blocking) or places impulses into the ventricular absolute refractory period (ventricular synchronous) until the intervals between spontaneous ventricular activity increase beyond the preset level Should atrial activity be intermittently conducted to the ventricle alternation between pacemaker produced and spontaneous contractions occur A ventricular synchronous ECG has spontaneous complexes with superimposed pacemaker stimuli and pacemaker produced complexes as well (Fig 6)

Atrial arrhythmia with drug induced varying conduction Six patients with supraventricular tachycardia and block of either spontaneous origin or induced by propranolol quinidine digoxin or combinations of drugs have been treated Tachycardia has been controlled by the production of an A V block with intensive drug therapy Periods of asystole resulting from the block itself have been controlled with the pacemaker.[4]

Sinoatrial arrest Three patients with sinoatrial arrest have been treated In two stimulation of the atrium produced an effective conducted atrial beat and eliminated periods of asystole. However direct ventricular pacing was chosen because (1) the deleterious effect of possible late development of atrioventricular block was eliminated (2) atrial stimulation resulted in intermittent stimulation of the right phrenic nerve with diaphragmatic twitch (3) the long term effects and consistency of ventricular stimulation are better understood than those of atrial stimulation and (4) the ventricular effect of other atrial arrhythmias was more easily controlled with drug therapy (Fig 7)

Clinical experience

In implanting 52 demand (standby) pacemakers (30 stimulus blocking mode Ventricor II)*[7] 22 ventricular synchronous (Ectocor) the internal jugular vein was used once the external jugular vein twice and the cephalic vein 48 times for placement of the electrode catheter All the pacemakers but one were implanted in the subcutaneous tissue of the anterior chest wall.[7] One patient could not be consistently stimulated from the right ventricular endocardium and underwent direct myocardial pacer implantation

The stimulus blocking circuit was withdrawn from evaluation because of reports to the manufacturer of its sensitivity to extraneous radiofrequency and electrical stimuli with consequent suppression of pacer function and resultant ventricular asystole.[8] Neither suppression of function of the stimulus blocking pacer nor increase in rate of the ventricular synchronous pacer has occurred in our series.

Thus the ventricular synchronous unit (Ectocor) is now used It, too is capable of responding to extraneous electrical or radio-frequency stimuli but does so by increasing its rate to a maximum of 125 impulses per minute a circumstance we deem less dangerous even when sustained for several minutes than cessation of pacer function This event too, has not occurred in our group of patients

The longest duration of implant of the stimulus blocking unit is 14 months the

*Cord. Corporation, Miami, Fla

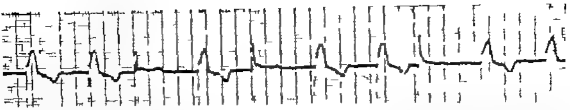

Fig. 6. During atrial fibrillation with ventricular response, the pacer rate will exhibit complete irregularity as it responds to conducted complexes and produces pacer complexes at its escape interval with the failure of A-V conduction.

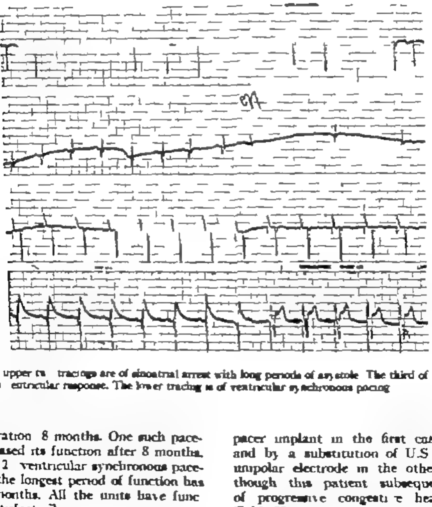

Fig. 7. The upper two tracings are of sinoatrial arrest with long periods of asystole. The third of pacing of the atrium with ventricular response. The lower tracing is of ventricular synchronous pacing.

mean duration 8 months. One such pacemaker ceased its function after 8 months.

Of the 2 ventricular synchronous pacemakers the longest period of function has been 6 months. All the units have functioned satisfactorily.

Complications

Early failures. Four early postoperative pacing failures were observed. Two were electrode failures in which consistent stimulation could not be achieved with the conventional endocardial electrode. Nevertheless it was attained by a myocardial pacer implant in the first case (P. D.) and by a substitution of U.S.C.I. C 50* unipolar electrode in the other (A. C.) though this patient subsequently died of progressive congestive heart failure (Table II).

There was one instance of perforation at the right ventricular apex. The electrode was withdrawn into the ventricular apex and pacing has since been consistent and stable.

*United States Catheter and Instrument Company, Glens Falls, N. Y.

Table II *Complications*

Patient	*Complication*	*Correction*	*Result*
J A	Perforation of apex with cessation of pacing	Electrode withdrawn int heart with resumption of pacing	L nd W
M B	Displacement of electrode from apex of right entricle—7 months after implant	Replacement of electrode into apex	I and W
C. G	Displacement of electrode from apex of right entricle during recurrent supraventricular tachycardia	Replacement of electrode into apex	L nd W
M K	Fract re of electrode in subcutaneous pocket following twisting	Repair	L nd W
M L.	Threshold increase—6 mm. long electrode	Replacement with 4 mm long electrode	L and W
P D	Inability t establish consistent transvenous pacing	Thoracotomy implant	I and W
A C	Inability t establish consistent pacing ith con entional electrode	Consistent pacing w th U.S.C.I C 50	Survived Died of congested heart failure
R W	Pacer failure—low output 8 months post implant	Replacement	L and W
S. K.	Electrode twist with impending fracture	Electrode resutured to pectoral fascia	L and W

Table III *Patient statistics*

L it	*N of patients*	*Mea ge*	*Sex*
Ventricor II (127A) timulating blocking	30	69 5	16 M 14 F
Ectocor (129A) ventricular synchronous	22	70 5	12 M 10 F
Total	52		

One early threshold increase above the output capability of the pulse generator occurred The problem was corrected with a newer now standard electrode and has not recurred

A subcutaneous electrode twist occurred one month following implant when one subcutaneous stay suture loosened This was corrected by secondary operation and resuture

Late complications One stimulus blocking (Ventricor II) pulse generator failed at eight months when its output fell below the endocardial threshold of response No other circuit failures have been found

Two patients ejected the electrode from the right ventricular apex. One ejection occurred seven months after implant on no apparent basis, the second during an episode of supraventricular tachycardia following the patient s unauthorized cessa tion of propranolol administration Both of these electrodes were of an older variety now superseded by an electrode with a 1 mm wide rubber flange just proximal to the metallic tip designed to increase fixity into the neo-endocardium

One electrode fractured in the subcutaneous tissue four months after implant. It had undergone axial torsion in the subcutaneous pacemaker pouch and fractured at the tightest point of the twist Steps have been taken to prevent such a future occurrence by suturing the electrode to the pectoral fascia until the growth of fibrous tissue limits electrode motion

There were two deaths. S. W a 48-year-old Caucasian man developed intermittent heart block following an embolus to a coronary artery from a prosthetic mitral valve The embolus produced a massive myocardial infarction He was resuscitated with residual intermittent block. Six weeks following pacer implant he died suddenly presumably of ventricular fibrillation. The autopsy revealed

fresh mitral valve thrombi without evidence of coronary artery embolism an electrode beginning to adhere to the tricuspid valve a pacemaker system functioning well electrically and an electrode appropriately placed.

A. C. was a 71 year-old Caucasian man with intermittent heart block, a slow nodal cardiac rhythm congestive heart failure, and cardiac cachexia. Increasing his cardiac rate did little to improve his status and he died of progressive congestive heart failure seven months following pacemaker implantation

Summary

A total of 52 patients have been treated for a variety of spontaneous or drug induced arrhythmias, all of which have been characterized by intermittently conducted atrioventricular activity Table III Each has had a demand (standby) pacemaker either of the stimulus blocking or ventricular synchronous variety Both varieties have proved themselves to be useful and to be relatively free of pulse generator difficulties. Electrode complications account for eight of the complications in this series.

REFERENCES

1. Nathan, D. A. Center S., Wu, C. Y. and Keller W. An implantable synchronous pacemaker for the long-term correction of complete heart block, Circulation 27:682, 1965.
2. Lemberg L., Castellanos, A Jr and Berkovits, B. V. Pacemaking on demand in A V block, J.A.M.A. 191 12, 1965
3. Furman, S Escher D J W Solomon, N and Krauthamer M: Electrocardiographic manifestation of standby pacing, Thoracic & Cardiovas. Surg [illegible] 723 1967
4. Furman, S., Escher D J W and Solomon, N. Standby pacing for multiple cardiac arrhythmias, Ann. Thoracic Surg 3:327 1967
5. Parsonnet, V Zucker I R., Gilbert, L., and Myers, G. H Clinical use of an implantable standby pacemaker J.A.M A. 196 103, 1966.
6. Furman S. Fundamentals of cardiac pacing Am. Heart J 73:261 1967
7. Denoth, F and Donato, L. A. Self-synchronizing cardiac pacemaker IEEE Trans. Bio-Med Engineering 14 103 1967
8. Personal communication—Cordis Corporation, Miami, Fla.
9. Meckstroth, C. V Schoenfeld, M. D and Wardwell, G. A Myocardial perforation from a permanent endocardial electrode, Thoracic & Cardiovas Surg 54 16, 1967
10. Danielson, G K., Shabetai, R and Bryant, L. R. Failure of endocardial pacemaker due to late myocardial perforation Successful restoration of cardiac pacing by conversion to an epicardial system Thoracic & Cardiovas. Surg 54:42, 1967

Pulmonary valve fusion with intact ventricular septum

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Pulmonary valve fusion with intact ventricular septum is an uncommon form of cyanotic congenital heart disease where there is complete obstruction to the outflow of the right ventricle by a diaphragm consisting of the fused cusps of the pulmonary valve. Blood flows from the right atrium through a patent foramen ovale or atrial septal defect into the left atrium and then to the left ventricle and aorta. The only supply to the pulmonary arteries is via a patent ductus arteriosus (Fig. 1). This condition has been called pulmonary atresia with intact ventricular septum, pulmonary atresia with normal aortic root,[1] and pulmonic atresia with intact ventricular septum.

The condition, although uncommon, is of interest and importance because early diagnosis, based on the clinical features, chest radiograph, and electrocardiogram (ECG), when confirmed by a selective angiocardiogram, may lead in some cases to successful treatment by immediate surgical intervention.

It has been recognized by others[2-4] that the patients fall into two categories: those with a hypoplastic right ventricular chamber and those with a normal or large right ventricular chamber. The distinction is important because the surgical approach and prognosis should be different in the two groups. It has been suggested that the groups may be differentiated during life by electrocardiography, radiological appearance,[3] or angiocardiography with assessments of the size of the right ventricular cavity.

Various aspects of this condition have been well described by others in the lit-

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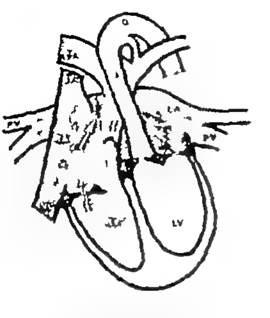

Fig. 1. Schematic diagram to show central circulation in pulmonary valve fusion and intact ventricular septum. *A*, aorta; *I*, inf. odiboluss; *IVC*, inferior vena cava; *LA*, left atrium; *LV*, left ventricle; *PV*, pulmonary vein; *RA*, right atrium; *RPA*, right pulmonary artery; *RV*, right ventricle.

few years.[5-8] We present our experience with 13 further cases which differ in some important respects from those already reported. These differences include the relative incidence of the two groups in this condition, some of the anatomical features especially relating to the tricuspid valve, our approach to the preoperative assessment of the right ventricular size, and the successful application of early closed transventricular valvotomy in the management of the cases with an adequate right ventricular chamber.

Materials and methods

Eleven patients with pulmonary valve fusion and intact ventricular septum were recognized during life at the Royal Alexandra Hospital for Children from May 1963 to October 1966. In addition, two patients were found in the review of the postmortem material of the hospital, one died with the condition undiagnosed in 1937 and the other in 1965. ECG's were usually standard 12 lead tracings. Some infants had only standard limb leads and V_1 and V or V \ and V_6 precordial leads recorded. Voltage evidence of hypertrophy was evaluated according to standards set out by various authors[9-11] as quoted by Guntheroth.[12]

Chest radiographs were exposed in the anteroposterior position with the patient supine at a focus-film distance of 48 inches. Angiocardiography was performed in ten cases using an Elema Schonander cut film changer (bi-plane). The injections were made selectively into the right ventricular chamber using a "Talley" injector with a gas cylinder pressure of 110 pounds per square inch and the changer programmed for 6 exposures per second for one second and 1½ exposures per second for six seconds. Kilovoltage ranged between 75 and 85 at 400 milliamperes for one hundredth of a second. In one case, cine angiocardiography was used.

During the examination, the diagnosis was confirmed by hand injections into the right ventricular chamber, the results being observed on the television monitor or recorded on videotape. For record purposes and for more precise analysis of the results, it was thought preferable to proceed to a definitive angiocardiogram.

Classification

On the basis of the operative and postmortem findings, the patients were classified into two groups as suggested by Greenwold and associates[1] according to the size of the right ventricular chamber. Group 1 included those with a small right ventricular chamber, and Group 2 included those with a normal or large right ventricular chamber. On this basis, four of our patients were in Group 1, eight of our patients were in Group 2, and the other (Case 10) was atypical and difficult to classify because there was a thin walled, large, low pressure right ventricular cavity. This patient, who developed atrial flutter at operation, was very similar to one described by Caddell and Whittamore.[13] These proportions are at variance with other series[1] where Group 1 patients comprised from 50 to 75 per cent of the total, although Schrire and co-workers described a series of three patients all of whom had a large right ventricle.

Clinical features

Our group of patients consisted of five boys and eight girls. One male and one female patient constituted a set of twins and had a sibling with severe pulmonary stenosis. There was no family history of congenital heart disease in any other patient. The age of presentation of the patients to us ranged from 2 days to 5 months; it was less than one month in ten of the 13 patients.

The more important physical findings are summarized in Table I. All of the patients were cyanosed in varying degree. A systolic murmur was heard at the left sternal edge in all patients, but a continuous murmur was heard in only one patient despite almost certain presence of a patent ductus arteriosus in all. In other series patients with no murmur were found[2,6] whereas sometimes continuous murmurs were heard.[3] In contrast to the findings of others,[4] congestive cardiac failure was thought to be present in only five of our patients. Respiratory distress was even less frequent; it was observed in

Table I

Case		Cyanosis (grade 0-4)	Congestive cardiac failure	Respiratory distress	Clinical cardiomegaly	Systolic murmur (grade 0-4)	Continuous murmur
1	C K	3	No	No	Yes	3	No
2.	M B	4	Yes	No	Yes	2	No
3	M B	4	Yes	Yes	Doubtful	2 3	No
4	S. R	1 2	No	No	Yes	3	Yes
5	D M	4	No	No	No	3	No
6.	B A.	4	No	No	Yes	2 3	No
7	N B	2	No	No	No	2–3	No
8	A P	3	Doubtful	No	Yes	2	No
9	W A.	4	Yes	Yes	Yes	3	No
10	J P	1 2	No	No	Yes	3	No
11	C B	3	No	No	Yes	3	No
12	P A.	2	Yes	No	Yes	3	No
13	S D	4	No	No	No	2	No

Table II

Case	Age	P waves (mm) (L_2 or V_1)	QRS frontal axis	Abnormal ventricular preponderance
1	3 wks.	2	+130°	No
2	11 wks.	5	+130°	Right
3	9 day	2	+ 70°	Left
4	2 day	3	+ 80°	No
5	11 wks.	2	+ 70°	No (hL left)
	5 mos.	4	+ 80°	Right
6	1 wk.	2	+ 80°	Left
7	3 days	3	+ 70°	No
8	2 wks.	3	+ 45°	Left
9	1 day	4	−110	No
10	1 wk.	5	+100°	Left
11	3 wks.	3	+150°	No
12	5 days	3	+140°	Right
13	6 day	5	+ 90°	Left

only two patients The clinical features were not helpful in the differentiation of patients in the two groups.

Electrocardiographic findings The relevant electrocardiographic findings seen preoperatively are set out in Table II The PR interval was normal for age and heart rate in all patients. Abnormal P waves of the pulmonale" type were present in almost all cases while electrocardiographic evidence of left atrial enlargement was not observed The QRS frontal axis was normal or right (+45 degrees to +150 degrees) in all cases but one where it was indeterminate (−110 degrees) Owing to the wide variation of the normal in infancy five of the ECG s were considered to show no definitely abnormal ventricular dominance Of the remaining eight, three showed abnormal right and five abnormal left ventricular preponderance for age. Examples are shown in Fig 2. The electrocardiographic criteria mentioned earlier were strictly followed in judging abnormal ventricular preponderance so that some cases which on inspection may have been judged to show abnormal left ventricular dominance for age (see Case 7 Fig 2) did not in fact fall outside the range of normality in this respect. Nonspecific ST-segment and T wave changes were seen in some cases.

In three out of five of the patients showing abnormal left ventricular preponderance the right ventricular chamber was small in one it was normal and in one (Case 10) it was a large abnormally thin walled low pressure chamber All of the

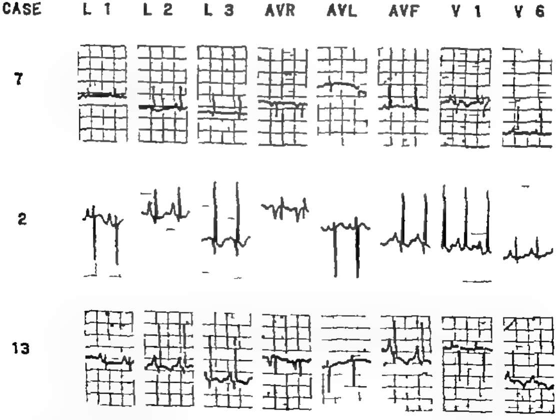

Fig. 2 ECG' from three of the cases. Patient 7 aged 3 days, showing no definitely abnormal ventricular preponderance. Right ventricle was normal in size. Patient 2, aged 11 wks showing abnormal right ventricular preponderance. Right ventricle as normal in size. Patient 13 aged six days, showing abnormal left ventricular preponderance. Right ventricle was small.

All three tracings show evidenc of right atrial hypertrophy

five patients with no definitely abnormal ventricular preponderance belonged to Group 2 as did two of the three infants whose ECGs showed right ventricular preponderance. The last patient with electrocardiographic evidence of right ventricular preponderance had a small right ventricular chamber. Thus, while the ECG may be helpful in differentiating Group 1 from Group 2 patients, exceptions occur in both groups as has been noted by others.

Radiology. As Keffer and Carey have stated, the most characteristic finding on the plain film is the diminution in the size of the pulmonary vasculature (Fig. 3). Cardiac enlargement was present in all cases. The degree of enlargement varied from slight to gross (Fig. 3). In most cases right atrial enlargement was demonstrable and this too varied from slight to gross in degree. Concavity of the superior portion of the left cardiac border[4] is present in some of the cases but is by no means a characteristic feature. The direction of the prominence of the lower left cardiac border is also variable in the present series. The most marked instance of cardiac enlargement was in the patient with a dilated low pressure right ventricle.

The findings of cardiac enlargement and decreased pulmonary vasculature in a cyanosed patient should bring the possibility of the diagnosis to mind. This suspicion, enhanced by the clinical and electrocardiographic findings, should lead to urgent cardiac catheterization and selective angiocardiography.

Cardiac catheterization and angiocardiography. Cardiac catheterization was performed on 11 of the 13 patients in this series primarily to obtain angiocardiograms. No extensive explorations with the catheter were carried out and only a limited number of blood samples were collected as in most cases the infants were very ill and minimal investigations were considered advisable. The right ventricle was entered in all cases. In 10 of the 11 patients, the right ventricular systolic pressure was 65 mm. Hg or higher (range 65 to 170 mm. Hg) and in the remaining patient (Case 10) it was 30 to 35 mm. Hg. In our experience the right ventricular pressure was no guide as to whether a case fell into Group 1 or Group 2. The right atrial pressure was often characterized by abnormally tall *a* waves. In the majority, a hand injection of contrast medium through the catheter with the tip placed in the right ventricle and observed on the television monitor showed a typical to-and-fro movement of the contrast medium across the tricuspid valve, while the left atrium, left ventricle, and aorta were outlined in turn with delayed filling of the pulmonary arteries. In a number of cases some of the contrast material remained for a considerable time in the cul-de-sac formed by the infundibulum and the fused pulmonary cusps, highlighting the lesion (Fig. 4).

The differentiation between Groups 1 and 2 by angiocardiography rests chiefly on the size of the right ventricular chamber *in relation to the size of the chest* rather than to the size of the heart. Aneurysmal dilatation of right atrium (see later) would make the latter comparison invalid.

In the Group 1 the ventricles were obviously small and the characteristic right ventricular shape was not evident (Fig. 5). In Group 2 the ventricles appeared to be of normal size and of relatively normal shape (Fig. 4). This differentiation has not been difficult in our experience.

Helpful additional information has been gleaned from the finding that in the two Group 1 patients with angiocardiograms, the infundibula were the smallest in the series and only in these two patients was there any injection of contrast material into the myocardium or into the myocardial sinusoids (Fig. 5) as described by Cornell.[16] In the anomalous case the pulmonary infundibulum was so enlarged that at first it was difficult to recognize it as this structure and not as part of a dilated right ventricle proximal to a more extensive form of pulmonary atresia (Fig. 6). In all the Group 2 patients, the infundibulum appeared adequate and the main pulmonary artery could be visualized to the pulmonary cusps, having filled from the aorta through the persistent ductus arteriosus. In one case the pulmonary cusps were sufficiently outlined for an estimate of their thickness to be made (Fig. 7). The diameter of the main pulmonary artery when compared with that of the aorta varied from less than half to approximately the same as the

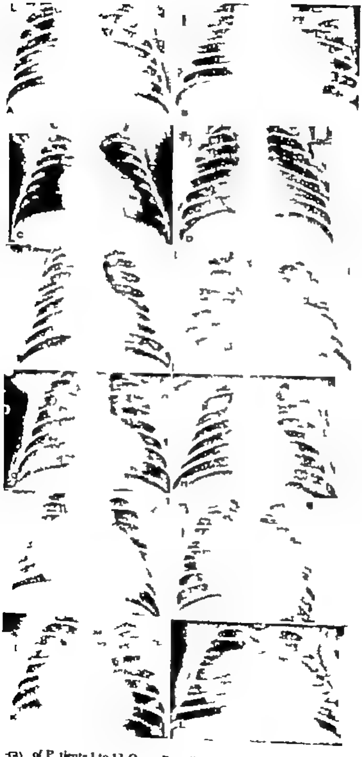

Fig. 3 A to *L*. Chest x-rays of patients 1 to 12. Over-all cardiac enlargement with some instances of aneurysmal enlargement of the right atrium. All x-rays show diminished pulmonary vasculature. F, H, and L are Group 1 patients. J is a typical patient.

Fig. 4. A, B, C, D, Case 5 and E, F, Case 3. A-P and lateral angiocardiograms, typical Group 2 patients. The right ventricle and infundibulum appear to be within normal limits for size and shape. In C and D exposed late in the series when there has been filling of the main pulmonary artery, contrast material has been demonstrated remaining in a cul-de-sac formed by fused cusps and infundibulum. *RA*, right atrium; *RV*, right ventricle; *I*, infundibulum; *A*, aorta; *LA*, left atrium; *LV*, left ventricle; *MPA*, main pulmonary artery.

aortic diameter, i.e., some pulmonary arteries were of normal size and some were small. All of the cases showed regurgitation of contrast material into the right atrium, which in some cases was only moderately enlarged, whereas in others the dilatation was aneurysmal in degree. The left atrium, left ventricle, and aorta were normal or slightly enlarged in all cases. A persistent ductus arteriosus was not demonstrated in all cases but its presence could be inferred from the opacification of the main pulmonary artery and its branches at a late stage of the angiocardiogram after opacification of the aorta. There have been no obvious ill effects after selective injection into the right ventricle and we feel that in order to be as certain as possible preoperatively of the diagnosis and of the differentiation into Group 1 or Group 2 that this is the angiocardiographic examination of choice.

Anatomical findings. The hearts were examined at necropsy in six of our patients.

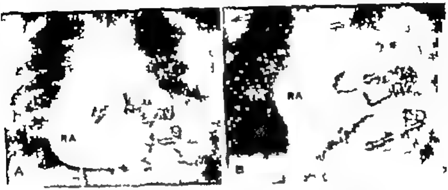

Fig. 5 (A), A.P. angiocardiogram Case 8. (B) A.P. angiocardiogram Case 6. The small size of the right ventricle and infundibulum in Group 1 patients is demonstrated. Also shown are the myocardial sinusoids filling from the right ventricle. I infundibulum. RA right atrium. RV right ventricle. S sinusoid.

Fig. 6 A.P. and lateral angiocardiogram, Case 10. The considerably dilated right ventricle and infundibulum (between arrows) are shown. RA right atrium. RV right ventricle.

Fig. 7 A.P. angiocardiogram, Case 11. The fused pulmonary valve cusps are outlined by contrast material in infundibulum from the right ventricular injection and by contrast material which has entered the main pulmonary artery from the aorta via patent ductus arteriosus. A aorta. I infundibulum. MPA main pulmonary artery. PVC pulmonary valve cusps. RA right atrium.

These included all four of our Group 1 patients and two Group 2 patients who were twins and did not go to surgery. All of the other Group 2 patients are alive except the atypical patient (Case 10) and one other, both of whom had postmortem examinations carried out in places other than our hospital.

The pulmonary arteries in the four Group 1 patients were hypoplastic, having a diameter of one seventh to one third of the diameter of the aorta, which was of normal size in all patients. In the Group 2 patients the pulmonary artery was approximately the same size as the aorta. In all the main pulmonary artery was patent throughout its length.

The pulmonary valve was totally obstructed in all cases and consisted of a

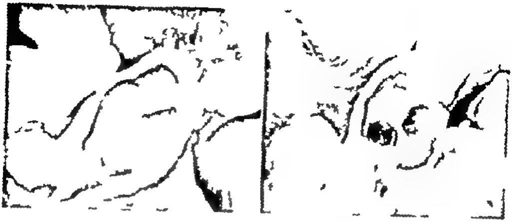

Fig. 8. Fused pulmonary valve cusps photographed from aspect of main pulmonary artery.

Fig. 9. Autopsy specimen of heart of Group 1 patient viewed from front and back. The small right ventricular cavity, narrow infundibulum, and relative sizes of pulmonary artery and aorta are demonstrated. The enlarged right atrium can be seen when viewed from behind. *A*, aorta; *LA*, left atrium; *LV*, left ventricle; *MPA*, main pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

diaphragm which on the arterial side had three ridges originating centrally and radiating to the wall of the pulmonary artery. Thus, the diaphragm appeared to represent the fused thickened three cusps of the pulmonary valve (Fig. 8). The diameter of the valve ring was either equal to or slightly smaller than that of the main pulmonary artery.

The right ventricular cavity was small in two and minute in the other two cases in Group 1. The thickness of the right ventricular wall was 4 to 5 mm. (Fig. 9). In the Group 2 babies, the right ventricular cavity was normal in size but the ventricular wall was grossly hypertrophied being 7 and 9 mm. thick (Fig. 10). The infundibulum in all six cases was somewhat narrowed but patent to the level of the valve.

The tricuspid valve was abnormal in all four Group 1 patients, the abnormality in each patient consisting of the septal cusp adhering to the ventricular wall as well as some thickening of all of the cusps along their free margins. The two Group 2 patients had apparently normal tricuspid valves (Fig. 10). No Ebstein-like deformity

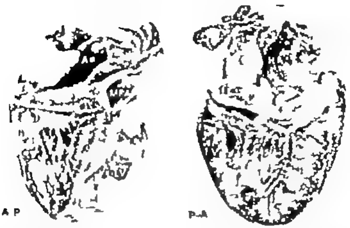

Fig. 10. Autopsy specimen of heart of Group 2 patient from front and back. The hypertrophied right ventricular wall, right ventricular cavity of normal size, normal tricuspid valve, and large main pulmonary artery (MPA) are demonstrated. From behind the dilated right atrium (RA) is seen. A, aorta; LV, left ventricle; RV, right ventricle.

Fig. 11. A P and lateral angiocardiogram, Case 5, postoperative. The bulk of the contrast material injected into the right ventricle (RV) passes through the pulmonary valve ring into the main pulmonary artery (MPA). There is still some regurgitation of contrast material into the right atrium (RA). Further operative procedures on the pulmonary valve and infundibulum (I) may be necessary at some future date. RPA, right pulmonary artery.

of the valve as described by Elliott and associates[8] was observed in any of our cases. The right atrium was enlarged in all patients, being enormous in size with a hypertrophied atrial wall in three of the four Group 1 patients.

An interatrial communication was present in all cases and consisted of a patent foramen ovale except in one case in Group 1 in which an atrial septal defect of the secundum type 10 mm. in diameter was present.

A persistent ductus arteriosus was present in all specimens, the internal diameter ranging from 1 to 3 mm.

Pulmonary venous drainage, left atrium, left ventricle, mitral valve, aortic valve, and aorta were normal in appearance in all cases. The coronary arteries were normal in all cases except one case belonging to Group 1 where the right coronary artery was short and nonfunctioning without communication with the aorta. This same patient was the only one with any associated congenital anomaly—a multicystic kidney being present.

Table III

Case	*Group*	*Age at operation*	*Result*	*Period of follow-up*	*Comment*
1	2	17 mo.	Survival	yr	Only slight initial improvement; subsequent general progress satisfactory but still has cyanosis Grade II marked cardiomegaly loud systolic, and continuous murmurs. Result fair
4	2	2 mo	Survival	$2\frac{1}{2}$ yr	Good immediate result subsequent progress satisfactory except for possible mental retardation and convulsions. Has only Grade I to II cyanosis slight cardiomegaly and loud ejection systolic murmur Good result
5	2	6 mo.	Survival	$2\frac{3}{4}$ y	Good immediate result angiocardiogram 1 mo. post operatively showed continuity from right ventricle to pulmonary artery (Fig 11). Subsequent general progress satisfactory Grade II cyanosis slight cardiomegaly and a loud ejection systolic murmur Good result
6	1	5 wk	Death at operation		Valvotomy difficult to achieve false passage created from right ventricle to pericardial sac
7	2	5 wk.	Survival	7 mo	Good immediate result subsequent progress good. Has only Grade I cyanosis, no cardiomegaly and soft systolic murmur Good result
8	1	2 mo	Late death at 9 mo.	7 mo	No real improvement course complicated by severe persistent wound infection. Death 7 mo. postoperatively
9	2	2 day	Death postoperatively		Excellent immediate result with loss of cyanosis. Reoperation within a few hours for hemorrhage Death
10		3 wk	Death at operation		Unusual case with dilated, thin-walled low-pressure right ventricle Atrial flutter followed by cardiac arrest at operation before valvotomy attempted
11	2	4 wk	Survival	1 mo.	Good immediate result cyanosis Grade II to I Loud ejection systolic murmur Good result

Course and management Four babies were not operated upon and death occurred in all of these at an age ranging from 8 days to 7 months.

Operation was carried out in the remaining nine In all of them this consisted of a closed transventricular valvotomy A small incision with a tenotomy knife was made in the outflow tract of the right ventricle and the diaphragm of the fused valve cusps pierced by a curved sharp-pointed arteriotomy scissor and a small Brock valvulotome and then further dilated with Brock dilators. The ventriculotomy was then repaired

Supportive measures including oxygen digoxin and diuretics were used as indicated both in the preoperative and postoperative period

Our surgical experience is seen in Table III It shows that the Group 1 patients and the unusual Patient 10 died In Group 2 there were six patients operated upon with five survivors. The single death in this group was due to postoperative hemorrhage after an apparently excellent immediate result was achieved As we consider closed pulmonary valvotomy a palliative rather than a curative procedure, we regard survival with even slight improvement as a fair result while satisfactory development with markedly decreased cyanosis is classified as a good result. If cyanosis was completely absent and no signs of obstruction to right ventricular outflow were present the result would be excellent. By these criteria a good result was achieved in four of the survivors while in the re-

maining patient a fair result was achieved. The improvement in these cases following operation was immediate and was clearly attributable to the operation.

Discussion

The early diagnosis of pulmonary valve fusion is an important one in that at least some of the cases are potentially salvageable by timely surgical intervention and their prognosis without treatment is poor. The clinical features present no consistent picture except that all of the patients were cyanosed, had a systolic murmur, and very few had respiratory distress. We considered the murmur to be due to tricuspid regurgitation. The plain x-rays of the chest often raised suspicion of the diagnosis with invariable enlargement of the heart, evidence of right atrial enlargement, and diminished lung vascularity. P pulmonale in the ECG with either right, left, or equivocal ventricular preponderance and a normal or right QRS axis in the frontal plane heightened the degree of suspicion. These findings are all similar to those of other series.[2, 4] The final diagnosis in life, however, can be achieved only by angiocardiographic studies and was made in this way in 11 of our cases. Ten of these studies have been described in a previous communication.[4]

Other authors have stressed the division of these cases into two groups: (1) those with a small or minute right ventricle and (2) those with a normal or hypertrophied right ventricle.

Although only six autopsy specimens are available in our series, it appears probable that four of our 13 cases represent Group 1 while eight of our cases represent Group 2. Case 10 was unusual in that the right ventricular cavity was large, but the right ventricular muscle wall was thin and the right ventricular pressure was low. This patient was thus not classified in either group and appeared to be very similar to the case described by Caddell and Whittemore.[11] The high proportion of Group is at variance with that previously reported by most authors.[2]

The distinction between the two groups in life is most important if a logical surgical approach to this condition is to be formulated. It is clear that in Group a closed pulmonary valvotomy if satisfactorily performed will be lifesaving and it is equally clear that the same procedure is probably useless in Group 1, where the right ventricle is unable to handle an adequate cardiac output to the lungs and relief of right ventricular obstruction is difficult or impossible to achieve. Our surgical experience is in agreement with this, as the result with pulmonary valvotomy in Group 1 patients was invariably fatal. Therefore, while we would agree with the contention of Gross[17] and others that shunt procedures should be carried out in Group 1, we believe that closed pulmonary valvotomy is the procedure of choice in Group 2, where out of six patients there was only one operative death and four of the five survivors achieved a good result.

The technical difficulties in achieving an adequate valvotomy are emphasized by Case 8, where, despite an apparently successful procedure, autopsy examination showed an inadequate relief of obstruction (Fig. 12), and in Case 1, where signs of persistent severe obstruction to right ventricular outflow are still present. It is possible that the small opening made in the valve diaphragm by the tenotomy knife was temporarily stretched by the dilators but soon returned to pinpoint size.

It is accepted that closed transventricular valvotomy under these circumstances can only be regarded as a palliative procedure pending a formal open valvotomy at a later stage. However, it should be possible to improve the efficiency of the operation by designing scaled-down instruments appropriate to the small size of these infants. A small Brock valvulotome and a small Brock dilator have already been made and used. A small two-bladed expanding dilator would also be a valuable additional instrument.

The clinical distinction of Group 1 from Group 2 may be attempted on electrocardiographic features, radiological appearances, cardiac catheterization findings, or an estimate of right ventricular cavity volume on the angiocardiogram. We have not found radiological features or right ventricular pressure readings obtained at cardiac catheterization of any assistance except that low right ventricular pressure sug-

Fig. 12. Case 8. Inadequate pulmonary valvotomy viewed from (A) above and (B) below. A, The siting of valvotomy close to the pulmonary ring can be seen (crossed arrow). B, The inadequacy of the outflow tract is apparent (arrow). PVC, pulmonary valve cusps; RV, right ventricle.

gests an atypical situation. The ECG was helpful in that most patients showing evidence of abnormal left ventricular preponderance belonged in Group 1, while most of those showing right or no abnormal preponderance belonged in Group 2. This correlation was enhanced if strict criteria previously mentioned were used in judging abnormal ventricular dominance. However, exceptions occurred in both groups, as has been the experience of others.

Angiocardiographically, the differentiation into the two groups basically rests on the subjective assessment of whether the right ventricle is of adequate size for the patient's chest, and this has correlated well with operative and autopsy findings. A comparison of the size of the right ventricle to that of the left ventricle on the angiocardiogram is another possible method of assessment but was not explored in this study.

It should be stressed that the investigation of these infants should not be delayed and should be followed as soon as possible by appropriate operation as they are dependent for life on the patency of the ductus arteriosus and may die suddenly, presumably owing to the closure of the ductus, despite an initially satisfactory condition, as happened in two of our Group 2 infants.

An unusual anatomical finding in our series was that the tricuspid valve appeared normal in the two Group 2 patients which came to necropsy, while in all of the four Group 1 patients it was abnormal. This is at variance with the findings of others who found that in Group 1 the valve was small but competent and normal in appearance, while in Group 2 it was incompetent and abnormal. Elliott and associates, however, found that in seven of their nine Group 1 patients the tricuspid valve was abnormal. In fact, these and other authors ascribe the different pathogenesis of the two groups of patients to the abnormalities of the tricuspid valve with incompetence in Group 2 and a competent tricuspid valve in Group 1, but this did not appear to be true in our series. It is possible that Group 1 represents a form of right heart hypoplasia, while Group 2 is the extreme form of pulmonary valve stenosis. In other respects, the anatomical findings in our patients showed no significant differences from those of others.

Summary

Thirteen patients with pulmonary valve fusion and intact ventricular septum have been studied. The clinical, radiological, and electrocardiographic features are described. The patients were divided into Group 1 (four patients with small right ventricle) and Group 2 (eight patients with normal or large right ventricle), while one patient was atypical.

The importance of differentiating between Groups 1 and 2 during life is emphasized. The ECG is helpful, but not unerring, in this respect. An estimate of right ventricular cavity size on the angiocardiogram appears to be the most reliable method.

Nine of the patients had closed pulmonary valvotomy carried out. Six of these were Group 2 patients of whom five survived four with good results and one with a fair result.

Closed pulmonary valvotomy is an excellent palliative procedure in Group 2 patients but of no real benefit in Group 1 patients. Consideration should be given to shunt procedures in the latter group. Surgery should be performed as soon as possible after definitive diagnosis.

The anatomical features of the six patients which came to autopsy are described and compared with the findings of previous authors.

REFERENCES

1. Greenwold, W. E., DuShane, J. W., Burchell, H. B., Bruwer, A., and Edwards, J. E.: Congenital pulmonary atresia with intact ventricular septum: two anatomic types, Circulation 14:945, 1956.
2. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1958, The MacMillan Company, p. 569.
3. Nadas, A. S.: Pediatric cardiology, Philadelphia, 1963, W. B. Saunders Company, p. 634.
4. Davignon, A. L., Greenwold, W. E., DuShane, J. W., and Edwards, J. E.: Congenital pulmonary atresia with intact ventricular septum: clinicopathologic correlation of two anatomic types, Am. Heart J. 62:591, 1961.
5. Benton, J. W., Jr., Elliott, L. P., Adams, P., Jr., Anderson, R. C., Hong, C. Y., and Lester, R. G.: Pulmonary atresia and stenosis with intact ventricular septum, Am. J. Dis. Child. 104:161, 1962.
6. Elliott, L. P., Adams, P., Jr., and Edwards, J. E.: Pulmonary atresia with intact ventricular septum, Brit. Heart J. 25:489, 1963.
7. Schrire, V., Sutin, G. J., and Barnard, C. N.: Organic and functional pulmonary atresia with intact ventricular septum, Am. J. Cardiol. 8:100, 1961.
8. Gasul, B. M., Arcilla, R. A., and Lev, M.: Heart disease in children, Philadelphia, 1966, J. B. Lippincott Company, p. 714.
9. Ziegler, R. F.: Electrocardiographic studies in normal infants and children, Springfield, 1951, Charles C Thomas, Publisher.
10. Manning, G. W., and Smiley, J. R.: QRS voltage criteria for left ventricular hypertrophy in a normal male population, Circulation, 29:224, 1964.
11. New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels, New York, 1953, New York Heart Association.
12. Guntheroth, W. G.: Pediatric electrocardiography, Philadelphia, 1965, W. B. Saunders Company, p. 27.
13. Caddell, J. L., and Whittemore, R.: Pulmonary atresia with dilated right ventricle: a case with congenital atrial flutter, Am. J. Cardiol. 12:254, 1963.
14. Kieffer, S. A., and Carey, L. S.: Radiological aspects of pulmonary atresia with intact ventricular septum, Brit. Heart J. 25:655, 1963.
15. Cornell, S. H.: Myocardial sinusoids in pulmonary valvular atresia, Radiology 86:421, 1966.
16. Grattan-Smith, P., Celermajer, J. M., Bowdler, J. D., and Gengos, D. C.: Pulmonary valve atresia with intact ventricular septum. A series of ten cases examined by selective angiocardiography, Australian Pediat. J. 2:237, 1966.
17. Gross, R. E.: Presidential address—Thoracic surgery in infants, J. Thoracic & Cardiovas. Surg. 48:152, 1964.

The hemodynamic effects of ouabain upon the diseased left ventricle

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Failure of the cardiac output in normal human subjects to increase in response to digitalis[1] has been interpreted as indicating an absent or negative inotropic response. More adequate assessment of myocardial contractility, however, by measurement of muscle tension,[2] or velocity of muscle shortening[3] in man, and by means of ventricular function curves in dogs[4] has established that digitalis glycosides have a positive inotropic effect upon the normal heart.

Most patients with congestive heart failure collected from the literature have been found to increase cardiac output in response to digitalization.[5] Yet a number of patients failed to do so.[6] However, most studies of the acute hemodynamic effects of digitalis glycosides have focused upon the right ventricle, even when the disease studied involved primarily the left ventricle.

In view of the present concepts of the inotropic action of digitalis, it seemed appropriate to re-examine the hemodynamic effects of acute digitalization upon the diseased heart. The present report analyzes the hemodynamic effects of ouabain in left ventricular disease.

Material and methods

Patients. A total of 20 patients in regular sinus rhythm form the main part of the study. Statistical analyses were based on this group. In addition, 3 patients in atrial fibrillation were studied, and 3 patients in regular sinus rhythm were restudied. These studies were considered separately.

Of the 20 patients in sinus rhythm, 14 had left ventricular pressure overload due

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to aortic stenosis or hypertension When present aortic stenosis was severe with a calculated valve area of 0.5 to 0.9 sq cm Hypertension varied from mild to severe but in all patients so diagnosed several diastolic blood pressures above 95 mm Hg were recorded. Two patients (Nos. 7 and 9) had normal blood pressures at the time of their study

The 6 patients with myocardial disease had either idiopathic myocardial disease or old myocardial infarct. Three patients had idiopathic myocardial disease. The diagnosis in two of them was quite certain on the basis of typical clinical course, absence of any other diseases by known tests including the use of coronary angiography in one of these patients (No 10) the diagnosis was confirmed at autopsy The diagnosis of the third patient (No 18) was on somewhat less secure grounds. In the 3 patients with old myocardial infarct, the diagnosis was clear clinically and electrocardiographically one patient (No 20) had mild exertional angina as well

None of the patients had significant valvular regurgitation anemia fever thyroid disease or other known complicating disease except Patient 12 who had mild aortic valvular stenosis in addition to myocardial infarct and Patient 22 in the group with atrial fibrillation who had evidence of coronary artery disease in addition to hypertension.

Cardiac size was estimated on the basis of physical examination and chest roentgenogram A scale of 1 plus (minimal enlargement) to 5 plus (huge heart) was used.

The functional capacity of each patient was determined by using the criteria of the New York Heart Association (NYHA)[11] Of the 20 patients in regular sinus rhythm 1 had moderate or severe exertional dyspnea (functional class III or IV) and 8 had no or mild exertional dyspnea (functional class I or II) The patients were classified on the basis of fatigue and exertional dyspnea since only one patient had angina (mild) and no patient complained of palpitation as his main symptom The determination of the functional class of a patient was based upon follow-up over several weeks or months prior to study

All patients were hospitalized for 1 to 3 days prior to study except for 7 patients in class III or IV (Nos. 4 6 7 7a 10 10a 11 12 and 22) who were hospitalized for one to several weeks until their weight and clinical condition were stable. These patients were treated initially with bed rest and diuretics with or without cardiac glycosides. Several patients in class III or IV had never been digitalized and most of the digitalized patients had been receiving digoxin The study was performed when the patient either had received no digitalis or at least two weeks after digoxin or one month after digitoxin or digitalis leaf had been discontinued Diuretics were used sparingly or not at all for one week prior to the study except in hypertensive patients (Nos. 6 and 7) who were taking chlorothiazide Patients of the main study did not receive other antihypertensive drugs. Patient 9a was restudied while taking reserpine 0 25 mg twice per day

Procedure As part of diagnostic or preoperative evaluation and after informed consent had been obtained right and left heart catheterization was performed while the patient was in the fasting state for the most part without any sedation Left heart catheterization was performed by one of three routes transdorsal transseptal or retrograde. Right heart catheterization was performed through a number 8F or 9F Cournand catheter from the left antecubital vein Systemic arterial pressures and blood samples were obtained from the brachial artery through a 17 gauge Cournand needle The central venous pressure was recorded through a polyethylene catheter (PE 160 internal diameter 0 045 in) inserted from the arm into the superior vena cava

Cardiac output was measured by means of the indicator dilution method[12] using the Colson densitometer[14] and the integrated sample technique for calibration blood was drawn f om the brachial artery by a constant withdrawal pump (Harvard Apparatus Company) at a ate of 35 ml per minute Approximately 3 mg of indocyanine green dye were injected into the superior ena cava from a calibrated pipette followed by a 10 ml. saline flush Pressures were measured by Statham P 3D or G strain gauges and recorded on a Sanborn multichannel direct or photo-

graphic recorder. The zero reference level was 10 cm. from the patient's back. Mean pressures were obtained by electrical damping.

Control cardiac output was measured in duplicate approximately 10 minutes apart. Then ouabain, 0.4 to 0.75 mg., was given intravenously over 3 minutes. Cardiac output was measured in general 30 and again 45 minutes after completing the injection of ouabain. Pressures were always recorded immediately following the measurement of cardiac output as well as at 10 and 20 minutes after the administration of ouabain.

Lead II of the electrocardiogram (ECG) was monitored continuously. The catheters were kept patent by very slow infusion of 5 per cent dextrose in water.

Measurements. Direct measurements were made of the heart rate (HR), left ventricular systolic pressure (LV s), left ventricular end-diastolic pressure (LV ed), brachial arterial systolic, diastolic, and mean pressures (BA syst., BA diast., and BAm), pulmonary arterial systolic, diastolic, and mean pressures (PA syst., PA diast. and PAm), and mean central venous pressure (CVP). Left ventricular systolic mean pressure (LV syst. m.) was measured in patients with aortic stenosis by manual integration of the area of several left ventricular pressure curves during systolic ejection or in patients without aortic stenosis by manual integration of several brachial arterial pressure curves during systole, between the beginning of pressure rise and the dicrotic notch. Right ventricular systolic mean pressure (RV syst. m.) was calculated similarly from the pulmonary arterial pressure tracings. Left ventricular diastolic mean pressure (LV dm) was measured by integrating manually the diastolic phase of several left ventricular pressure curves. The maximal rate of left ventricular systolic pressure development (LV dp/dt) was obtained manually from the greatest ascending slope of the left ventricular curve, expressed in millimeters of mercury per second. This occurred mostly during the latter part of the isovolumic contraction period. The recording system used does not permit valid measurement of absolute dp/dt. This measurement was used strictly for purposes of comparison of values obtained in identical manner in the control state and after administration of ouabain. This method has been shown to give correct directional changes.[15]

Cardiac index (CI) was calculated by dividing the cardiac output (CO) by the body surface area, stroke index (SI) by dividing the CI by the HR. Ventricular work was calculated from the net ventricular force during ejection and the stroke volume using the following formula: left ventricular stroke work index (LV SWI in grammeter per beat per square meter) = SI × (LV syst. m. − LV dm) × 1.055 × 0.0136.[1] Similarly, right ventricular stroke work index (RV SWI) = SI × (RV syst. m. − CVP) × 1.055 × 0.0136. Total peripheral resistance (T. Periph. R. in dyne-sec.-cm^{-5}) was calculated from the formula $\frac{\text{BAm} \times 60 \times 1{,}332}{\text{CO}}$.

Analysis of data

GROUP ANALYSIS. For statistical purposes one control value of a given parameter was used. When two measurements were made during the control period, the average was used. Clinically, the patients were divided into two groups: those who were in functional class III or IV and those who were in class I or II. Hemodynamically the patients were divided into two groups: those who had LV ed pressures above 12 mm. Hg (approximate upper limits of normal) and those who had LV ed pressures of 12 mm. Hg or below.

Comparison of a parameter during the control period in the different groups and subgroups was made by Student's "t" test, provided the group comprised at least 4 patients.

Comparison of the group's response to ouabain was made for each time-period after ouabain by Student's paired "t" test.[16]

When present, changes were evident at any time during the 20 to 70 minute period (Figs. 1 and 2), often at 10 minutes as well. Such a time-course has been noted also by others.[8] It was felt that for a given patient the average of several values was more accurate than one single value. Therefore, in addition to comparison of specific time periods after ouabain, the average

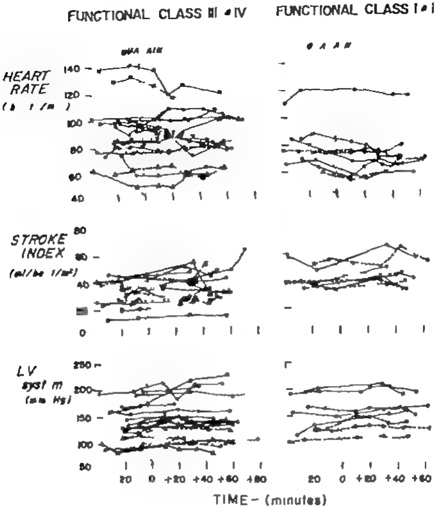

Fig. 1. Left ventricular function (the amount of blood ejected and the ejection pressure) before and after ouabain, administered at time zero.

Dots: patients in regular sinus rhythm; *squares*: patients in atrial fibrillation; *triangles*: repeat studies; *solid lines*: patients with left ventricular pressure overload; *interrupted lines*: patients with myocardial disease. Each line connects serial measurements in the same patient. Discussion in text.

of all values 20 to 70 minutes after ouabain and also the average of the values at the time period of the CO measurement was compared to the control. Tables III to VI present the results of the 20 to 70 minute period comparison; the results for the other time periods were essentially the same.

Analysis of individual patients. For the individual patients, Tables III and IV indicate whether the average (20 to 70 minutes) value after ouabain was higher (+) or lower (−) than the average control value.

INOTROPIC RESPONSE. Inotropic response was defined in terms of ventricular stroke work and ventricular end-diastolic or filling pressure. A patient was considered to have a positive inotropic response if stroke work increased at the same or lower end-diastolic and/or filling pressure, or if the stroke work did not change but the end-diastolic and/or filling pressure decreased. These changes had to be present (1) during most of the time-periods after ouabain, and (2) during the combined 20 to 70 minute period. A patient was considered to have a negative inotropic re-

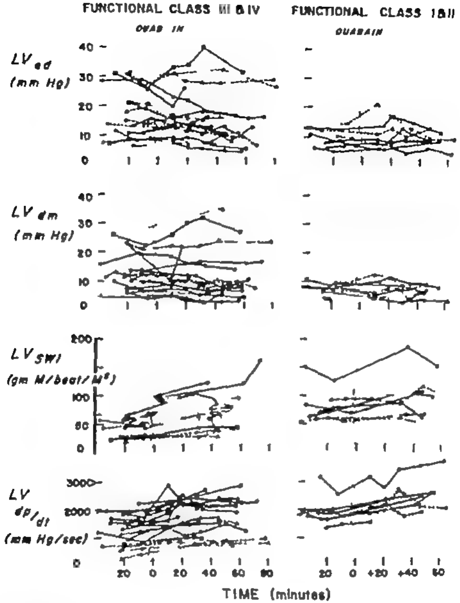

Fig. 2. Left ventricular function (the work and rate of pressure development as well as LV ed and mean diastolic pressure) before and after ouabain. Symbols as in Fig. 1.

sponse if stroke work decreased at the same or higher end-diastolic and/or filling pressure or if stroke work did not change at higher end-diastolic and/or filling pressure. A patient's inotropic response to ouabain could not be evaluated and therefore was termed indeterminate when the stroke work and end-diastolic or filling pressure changed concordantly or when changes were minor and variable.

NORMAL VALUES. The following approximate normal ranges were derived from a combination of values from the literature and experience in this laboratory. HR = 60 to 82 beats per minute. CI = 2.50 to 4.50 L. per minute per square meter. SI > 30 c.c. per beat per square meter. BA syst = 100 to 150 mm. Hg. BA diast. < 95 mm. Hg. LV SWI = 40 to 80 gram-meters per beat per square meter. LV ed < 12 mm. Hg. LV dm < 10 mm. Hg. PA syst < 30 mm. Hg. PAm < 20 mm. Hg. T. Periph. R < 1,800 dyne-sec.-cm.$^{-5}$

Results

Table I summarizes the clinical status the more important hemodynamic parameters in the control state and the inotropic responses to ouabain for each patient. Table II contains individual detailed hemodynamic data.

Left ventricular function.

RESPONSE TO OUABAIN IN RELATION TO CLINICAL STATUS.

Functional class. The response to ouabain of all patients with moderate or severe exertional dyspnea was as follows (Table III Figs. 1 and 2) The HR did not change, but the CI increased The SI LV syst. m pressure, LV SWI and LV dp/dt increased while LV ed and LV dm pressures fell. Therefore, in patients with moderate or severe exertional dyspnea as a group a positive left ventricular inotropic response was present.

Seven of the 8 patients in functional class IV and 2 of the 4 patients in functional class III (Table I) had a positive inotropic response as defined No patient had a clear negative inotropic response.

Patients with no or mild exertional dyspnea, as a group (Table IV Figs. 1 and 2) showed a positive left ventricular inotropic response as well LV SWI increased and LV ed pressure did not change. Examining each patient individually (Table I) 3 of the 8 patients in functional class I or II showed a positive left ventricular inotropic response Again no patient had a clear negative inotropic response.

Disease. When the patients were divided into those with left ventricular pressure overload and those with myocardial disease (Figs. 1 2 and 4) after ouabain in the overload group LV SWI increased ($P < 0.01$) while LV ed pressure did not change significantly in the myocardial disease group left ventricular stroke work increased ($P < 0.05$) while LV ed pressure fell ($P < 0.02$)

In the class III or IV category (Table I) 4 of 5 patients with aortic stenosis 2 of 4 patients with hypertension (therefore 6 of 9 patients with left ventricular pressure overload) 2 of 2 patients with idiopathic myocardial disease and the 1 patient with old myocardial infarct (therefore, 3 of 3 patients with myocardial disease) had positive left ventricular inotropic responses.

In the class I or II category (Table I) 1 of 2 patients with aortic stenosis, none of 3 patients with hypertension (therefore 1 of 5 patients with left ventricular pressure overload) the 1 patient with idiopathic myocardial disease and 1 of 2 patients with old myocardial infarct (therefore 2 of 3 patients with myocardial disease) had positive left ventricular inotropic responses to ouabain.

RESPONSE TO OUABAIN IN RELATION TO HEMODYNAMIC STATUS BEFORE OUABAIN Before ouabain most patients in classes III and IV had elevated LV ed pressure, and most patients in classes I and II had normal LV ed pressure (Tables I III and IV Fig 2)

In Fig 3 the average control value representing a point on the Frank-Starling ventricular function curve is plotted for each patient. Neither a straight line, nor a parabola can be drawn. The failure to show a relationship with a positive slope between LV SWI and LV ed pressure can be due to any or all of these factors (1) descending slope of the Frank Starling curve (2) markedly lower myocardial contractility in the patients with elevated LV ed pressure, and (3) a poor relationship between LV ed pressure and diastolic fiber size when LV ed pressure is elevated

After ouabain while there was a general tendency for LV ed pressure to fall and LV SWI to increase (Fig 4) patients with elevated LV ed pressure as a group were characterized by a greater response to ouabain than patients with normal LV ed pressure

RESPONSE OF LV DP DT TO OUABAIN LV dp/dt increased in every patient after ouabain (Tables III and IV Fig 2) The increase in LV dp dt occurred without increase in HR BA diast. or LV ed pressure in the patients as a group. Changes in these parameters have been shown to affect LV dp dt.

However the increase in LV dp dt was accompanied by an increase in LV syst m. pressure. A linear relationship was

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Table I Clinical data salient control hemodynamic parameters and ventricular inotropic response

Pt. No.	Cath. No.	Age Race Sex	BSA (M^2)	Diagnosis	Func. class	Heart size: Ext	Heart size: C T ratio	ECG	CI ($L/min/M^2$)	LVED (mm. Hg)	LVDM (mm. Hg)	CVP (mm. Hg)	Ouabain dose (mg.)	LV inotr resp.	RV inotr resp.
Functional classes III and IV normal sinus rhythm															
1	779	38 W M	1.52	Aortic stenosis	IV	3+	0.50	LVH	3.80	31.0	23.0	9.0	0.50	+	Indet.
2	536	48 W M	1.71	Aortic stenosis	IV	4+	0.70	LVH	3.54	1.0	14.0	1.5	0.40	+	+
3	787	48 W M	1.86	Aortic stenosis	IV	3+	0.53	LVH	3.30	16.0	10.0*	3.0	0.50	+	n.d.
4	980	40 W M	1.70	Aortic stenosis	IV	3+	0.54	LVH	3.31	14.5	11.6	3.0	0.50	+	n.d.
5	1 088	44 W F	1.44	Aortic stenosis	III	2+	0.60	LVH	3.67	14.0	14.0	12.0	0.60	Indet.	n.d.
6	1 096	40 W M	1.79	Hypertension	IV	3+	0.57	LVH	2.53	23.8	18.9	4.2	0.60	+	Indet.
7	1 153	41 N M	1.74	Hypertension	IV	3+	n.d.	LVH	3.35	11.1	6.4	2.1	0.60	None	Indet.
8	1 030	48 N F	1.83	Hypertension	III	3+	0.62	Prob. LVH	3.50	9.9	6.9	3.6	0.75	Indet.	d.
9	1 188	33 N F	1.84	Hypertension	III	2+	n.d.	Prob. LVH	2.18	6.5	8.0	3.4	0.60	+	n.d.
10	1 080	43 N M	1.61	Idiopathic myoc. dis.	IV	3+	0.60	Prob. LVH	1.83	25.9	24.0	13.0	0.50	+	n.d.
11	1 020	56 W M	1.70	Idiopathic myoc. dis.	IV	3+	0.57	LBBB	2.29	14.6	12.1	4.5	0.60	+	+
12	1 057	44 W M	2.05	Old myoc. infarct	III	d.	n.d.	Anterosept. MI	3.16	13.3	12.3	10.0	0.75	+	n.d.
Functional classes I and II, normal sinus rhythm															
13	1 039	40 W M	1.83	Aortic stenosis	II	1+	n.d.	Prob. LVH	4.10	9.0	7.5	6.0	0.75	+	+
14	1 108	42 W M	1.77	Aortic stenosis	II	WNL	0.50	Prob. LVH	3.86	12.8	9.4	3.9	0.60	Indet.	+
15	1 106	37 N M	2.00	Hypertension	I	WNL	0.47	WNL	3.15	5.5	3.8	3.9	0.75	Indet.	n.d.
16	1 138	48 W M	1.68	Hypertension	I	WNL	0.43	WNL	3.00	6.5	4.0	4.1	0.60	Indet.	Indet.
17	1 188	48 N M	1.66	Hypertension	I	n.d.	n.d.	Non-spec. abn.	3.20	8.4	7.8	5.4	0.50	Indet.	n.d.
18	1 190	22 W M	2.05	Idiopathic myoc. dis.	I	1+	n.d.	Non-spec. abn.	4.07	9.9	4.8	2.2	0.60	+	Indet.
19	1 175	60 W M	1.73	Old myoc. infarct	I	WNL	n.d.	Inf. MI	1.99	14.5	9.6	4.6	0.60	+	d.
20	1 182	37 W M	1.94	Old myoc. infarct	I	WNL	0.41	Post. MI	3.09	12.5	7.5	5.5	0.60	Indet.	d.
Patients in atrial fibrillation															
21	1 082	60 W M	1.61	Aortic stenosis	III	3+	d.	LVH	2.47	7.9	7.0	3.0	0.60	+	n.d.
22	1 116	57 N M	1.94	Hypertension	IV	2+	0.66	Non-spec. abn.	1.80	23.5	24.0	24.5	0.75	Indet.	Indet.
23	1 011	45 N M	2.02	Idiopathic myoc. dis.	III	2+	0.57	Non-spec. abn.	2.64	40.9	23.5†	14.0	0.75	+	Indet.
Repeat studies, normal sinus rhythm															
9a	1 100	33 N F	1.77	Hypertension	III	2+	0.57	Non-spec. abn.	2.36	8.3	4.6	3.0	0.60	+	n.d.
10a	1 076	43 N M	1.61	Idiopathic myoc. dis.	IV	3+	0.60	Prob. LVH	2.40	33.0	31.0	18.0	0.60	+	Neg.
10b	1 119	44 N M	1.65	Idiopathic myoc. dis.	III	1+	0.53	LVH	2.30	18.5	12.8	3.5	0.60	+	+
7	1 191	41 N M	1.70	Hypertension	IV	2+	n.d.	LVH	3.35	d.	11.6‡	4.9	0.60	n.d.	Indet.

Abbreviations: BSA, body surface area; C. T. ratio, cardio-thoracic ratio; CI, cardiac index; LVED, left ventricular end-diastolic pressure; LVDM, left ventricular diastolic mean pressure; CVP, central venous pressure; LV inotr. resp., left ventricular inotropic response; RV inotr. resp., right ventricular inotropic response; LVH, left ventricular hypertrophy; Indet., indeterminate; LBBB, left bundle branch block; MI, myocardial infarction; WNL, within normal limits; Non-spec., non specific ST and T wave changes; and d., no data.

*Left atrial mean pressure = 11 mm. Hg.

†Left atrial mean pressure.

‡Pulmonary arterial wedge pressure.

Table III Left ventricular function before and after ouabain in patients with moderate or severe exertional dyspnea (functional classes III and IV)

	HR (beats/min.)	CI (L./min./M.²)	SI (ml./beat/M.²)	LV syst. m. (mm. Hg)	LV SWI (Gm.-M./beat/M.²)	LV ed (mm. Hg)	LV dm (mm. Hg)	LV dp/dt (mm. Hg/sec.)
Before ouabain								
Left ventricular overload (9 patients)								
Mean	91.0	3.25	36.2	163.0	78.8	17.0	12.4	1,659
S.D.	13.1	0.63	6.1	25.8	17.1	8.3	5.3	332
Myocardial disease N = 3								
Mean	80.7	2.43	30.5	91.0	31.6	15.9	16.1	678
Minimum	77	1.83	22.6	69.0	17.4	13.3	12.1	594
Maximum	[illegible]	3.18	41.6	105.0	47.0	25.9	24.0	731
All patients (12 patients)								
Mean	88.3	3.06	34.8	143.5	65.8	17.5	13.4	1,409
S.D.	10.8	0.64	7.2	40.1	25.9	8.1	6.0	563
After ouabain								
All patients* (12 patients)								
Mean	88.3	3.49	38.7	130.8	80.7	14.8	11.6	1,882
S.D.	12.0	0.80	6.6	27.8	13.0	6.6	5.3	637
P	NS	< 0.03	< 0.05	< 0.01	< 0.02	< 0.03	< 0.01	< 0.01
Number of patients showing change†								
Positive	7	10	10	12	10	2	1	12
Negative	4	2	2	0	1	10	11	0
None	1	0	0	0	1	0	0	0

Abbreviations: HR, Heart rate; CI, cardiac index; SI, stroke index; LV syst. m., left ventricular systolic mean pressure; LV SWI, left ventricular stroke work index; LV ed, left ventricular end-diastolic pressure; LV dp/dt, left ventricular maximum rate of change in systolic pressure; S.D., standard deviation; P, probability; and NS, not significant.

*For each patient, the average value of all measurements 20 to 70 minutes after ouabain—see "Methods."

†For each patient, the directional change of the average value of all measurements 20 to 70 minutes after ouabain compared to the average control value—see "Methods."

present between LV dp/dt and LV syst. m. pressure before ($r = 0.668$, $P < 0.01$) and after ($r = 0.577$, $P < 0.01$) ouabain. Many of the values after ouabain were above control but the difference in the regression lines was not statistically significant. Reeves and associates[8] in dogs found a linear relationship between LV dp/dt and LVs pressure with values above those expected from changes in LVs pressure alone when myocardial contractility was increased by epinephrine. LV syst. m. pressure has been used in our studies rather than LVs peak, because it is felt that this is a more accurate measurement even if influenced slightly by changes in ejection time.

In order to take advantage of the paired data and because a linear relationship was present between LV dp/dt and LV syst. m. if one assumes that for each patient such a linear relationship exists, then the ratio LV dp/dt/LV syst. m. can be compared before and after ouabain by Student's paired "t" test. This ratio increased significantly in both the class III or IV ($P < 0.02$) and class I or II (P <

*Table IV. Left ventricular function of patients with mild or no exertional dyspnea (functional classes I and II)**

	HR (beats/min.)	CI (L./min./M.²)	SI (ml./beat/M.²)	LV syst. m. (mm. Hg)	LV SWI (Gm. M./beat/M.²)	LV ed (mm. Hg)	LV de (mm. Hg)	LV dp/dt (mm. Hg/sec.)
Before ouabain								
Left ventricular overload (patients)								
Mean	[illegible] 0	3.4	41.6	166.0	93.8	8.4	6.6	2,093
S.D.	17.6	0.45	7.3	30.1	29.6	2.8	2.5	[illegible]
Myocardial disease (3 patients)								
Mean	68.0	3.03	43.3	113.7	69.8	12.3	7.3	1,734
Minimum	57	1.93	34.3	105	57.2	9.5	4.6	1,400
Maximum	76	4.18	56.2	126	84.1	14.5	9.6	1,899
All patients (9 patients)								
Mean	73.4	3.29	42.3	140.8	84.0	9.9	6.8	1,929
S.D.	17.7	0.69	7.7	34.8	27.7	1.2	2.3	412
After ouabain								
All patients (9 patients)								
Mean	74.0	3.[illegible]	46.4	158.1	97.7	10.1	6.3	2,435
S.D.	15.1	[illegible]	8.7	31.6	16.1	3.0	0.7	422
P	NS	NS	NS†	NS†	< 0.05	NS	NS	< 0.01
Number of patients showing change								
Positive	1	8	6	7	6	2	2	8
Negative	4	3	2	1	3	6	6	8
None	3	0	0	0	0	0	0	0

*For abbreviations and explanations, see Table III.
†0.05 < P < 0.1.

0.02) patients suggesting an increase in LV dp/dt beyond that expected from changes in LV syst. m. pressure alone.

Right ventricular function

RESPONSE TO OUABAIN IN RELATION TO CLINICAL STATUS. Patients with moderate or severe exertional dyspnea as a group showed an elevated RV syst. m. pressure and a generally elevated CVP (Table V). After ouabain only the CVP decreased. Inotropic response (Table I) was positive in 2 patients and indeterminate in 3. There were no patients with negative inotropic response.

In the functional class I or II patients (Table I) as a group RV syst. m., RV SWI and CVP were normal and did not change after ouabain. Inotropic response was positive in 2 patients and indeterminate in 2. There were no patients with negative inotropic response.

Comparison of left and right ventricular inotropic response. In 9 patients, data to determine both left ventricular and right ventricular inotropic response are available (Table I). In 5 of these patients there was a concordant change. In 3 the positive inotropic effect in the left ventricle was not evident in the right ventricle (Nos. 1, 6, and 18) and in one patient (No. 14) only the right ventricle showed a positive inotropic effect.

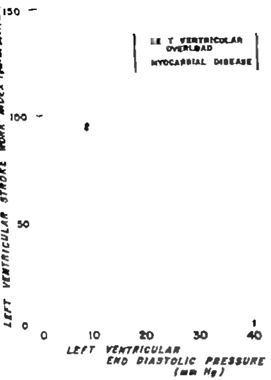

Fig. 3. Scattergram of points on the Frank-Starling ventricular function curves for all patients before ouabain. Patients are grouped into those with left ventricular pressure overload and those with myocardial disease. Each point represents the average control value for a single patient.

Effect of ouabain on T. Periph. R. and BA diast. pressure. After ouabain, no significant changes occurred. As a group, the patients with hypertension, as expected, had higher control T. Periph. R. and BA diast. pressures than the nonhypertensive patients (Table VI).

Patients in atrial fibrillation. All 3 patients in atrial fibrillation (Nos. 21, 22, and 23) were in functional class III or IV (Table I, Figs. 1 and 2). All had an elevated HR (mean 123 beats per minute) which, in contrast to patients with normal sinus rhythm, decreased after ouabain to a mean of 106 beats per minute. Two patients had a clear positive left ventricular inotropic response, while in one patient (No. 22) a marked increase in all pressures occurred.

Repeat studies. One patient had a restudy within one week (No. 10a) and again 6 months later (No. 10b) when he was clinically improved from class IV to class III (Table I, Figs. 1 and 2). The study within one week, like the original study, showed a markedly elevated LV ed pressure with low LV SWI before ouabain and a mild but definite positive left ventricular inotropic response to ouabain. Six months later the control LV ed pressure was lower but still above normal, the control LV SWI was higher, and the positive left ventricular inotropic response to ouabain was more pronounced. Restudy of the other two patients (Nos. 7a and 9a) at approximately the same clinical status showed essentially the same results as the original study.

Discussion

The Frank-Starling concept of myocardial contractility relates the energy to muscle fiber length.[19] The sensitivity and specificity of the method of measurement of myocardial contractility will depend upon how accurately it is possible to measure the energy of contraction and the initial fiber length.

When in our patients the energy of contraction was approximated by measuring left ventricular stroke work, and muscle fiber length by measuring LV ed pressure, increase in contractility was evident after ouabain in all patients with left ventricular disease as a group, regardless of type or severity, but the patients with more severe clinical disability, elevated LV ed pressure, and more abnormal control hemodynamic parameters were more likely to show a clear inotropic response. No patient had negative inotropic response (decrease in myocardial contractility).

Selzer and Malmborg, who studied a group of patients corresponding approximately to our class III or IV but more diverse, found that unequivocal hemodynamic improvement occurred in 10 of 15 patients. They used the increase in CO after intravenous digoxin as the most reliable index of digitalis effect. Of the 5 patients called "nonresponders," 2 had measurements of pulmonary wedge pressures which were normal at rest. One of these probably had a positive inotropic response to digoxin as judged by the relation of stroke work to end-diastolic

Table VI Peripheral vascular resistance

	Patients with moderate or severe dyspnea (classes III and IV)		*Patients with mild or no dyspnea (classes I and II)*	
	T Periph R (dyne-sec-cm⁻⁵)	*BA diast* (mm Hg)	*T Periph R* (dyne-sec-cm⁻⁵)	*BA diast.* (mm Hg)
Before ouabain				
Aortic stenosis				
Mean	1 229	67 8	1 195	80 5
S D	133	9 1		
Minimum			1 033	75
Maximum			1 357	86
N	5	5	2	2
Myocardial disease				
Mean	1 734	66 3	1 478	74 3
Minimum	863	61	957	73
Maximum	2 660	72	2 271	76
N	3	3	3	3
Hypertension				
Mean	2 016	98 5	1 925	104
S D	759	19 4		
Minimum			1 425	94
Maximum			2 355	127
N	4	4	3	3
All patients				
Mean	1 617	77 7	1 575	87
S.D	664	19 3	571	17 4
N	12	12	8	8
After ouabain				
All patients				
Mean	1 467	78 4	1 560	87 4
S.D	598	19	550	17 3
P	NS	NS	NS	NS
Number of patients showing change				
Positive	3	7	4	4
Negative	9	4	4	4
None	0	1	0	0

Abbreviations: T Periph. R., Total peripheral resistance; BA diast., brachial arterial diastolic pressure. For other abbreviations and explanations see Table III.
P = 0.05 < P < 0.1

rise to the present study,[2] namely, "to what extent does the nature of left ventricular disease and of left ventricular failure determine the inotropic effect of ouabain?" has been answered, at least qualitatively.

An increase in LV dp/dt measured by intracardiac pressure manometer was reported by Mason and Braunwald[4] in 4 patients with atrial septal defect who had never experienced congestive heart failure and whose LV ed pressures were normal. In these patients the LV ed pressure remained the same or decreased slightly. HR did not change and LVs pressure increased. With the use of a standard pressure transducer an increase in LV dp/dt was noted after acetylstrophanthidin

by Murphy and associates[15] in all 8 patients, and by Yu and co-workers[36] in all 7 patients studied.

Our studies demonstrate that a positive inotropic response was evident in all patients when myocardial contractility was measured by the relation of ventricular stroke work to end-diastolic pressure and by changes in LV dp/dt. The hemodynamic changes were more obvious in patients who had more severe functional impairment and more elevated LV ed pressure.

From studies of others it is likely that hemodynamic changes and therefore, measurement of myocardial contractility by the relation of stroke work to end-diastolic pressure in response to digitalis glycosides will depend at least in part on the influence of glycosides upon the peripheral blood vessels the degree of reflex adjustment possible and probably other variables. In addition the extent of changes in LV ed pressure may depend upon how much of the end-diastolic pressure represents myocardial failure (fiber length) myocardial restriction[19] or muscle stiffness.[20]

Summary

The evidence for left and right ventricular inotropic response to ouabain was examined in 20 patients in sinus rhythm. A total of 14 patients had left ventricular pressure overload from aortic stenosis or essential hypertension. Six patients had ischemic (old myocardial infarct) or idiopathic myocardial disease. The clinical severity of the disease varied from functional class I to IV. Myocardial contractility was estimated according to the Frank Starling concept, using ventricular stroke work and end-diastolic or filling pressure, and compared to changes in LV dp/dt.

It was concluded that myocardial contractility increased after ouabain in all patients but that this positive inotropic effect was not reflected with equal clarity in the classical hemodynamic measurements of CO ventricular filling pressure or even stroke work in relation to ventricular end-diastolic pressure.

In the class III or IV patients as a group a positive left ventricular inotropic response to ouabain was reflected in an increase in stroke work and a decrease in LV ed pressure. In the class I or II patients as a group a positive left ventricular inotropic response was present stroke work increased at unchanged end-diastolic pressure. Individually 9 of 12 patients in class III or IV and 3 of the patients in class I or II had a positive inotropic response. A positive inotropic response in the other patients was either not present or was not determinable. No patient had a negative inotropic response.

The hemodynamic pattern of patients in classes III and IV was more abnormal than that of patients in class I or II. As a group the class III or IV patients had elevated LV ed pressure and patients in class I or II had normal end-diastolic pressure. Thus the clinical classification correlated well with the control hemodynamic status.

After ouabain, there was an increase in LV dp dt in all patients this increase was out of proportion to the change in HR BA diast LV ed and LV s pressure. This finding confirmed the value of dp/dt as a measure of contractility.

The right ventricular hemodynamic parameters in general were less abnormal than the left. The right ventricle also showed evidence for a positive inotropic effect but less clearly so than the left ventricle.

The HR did not change after ouabain in the patients with normal sinus rhythm in contrast to the decrease observed in 3 patients in atrial fibrillation.

It is concluded that ouabain probably always has a positive inotropic action upon the diseased ventricle. However this action is reflected in the conventional hemodynamic measurements as a function of the clinical and hemodynamic status of the patient.

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REFERENCES

1. Adler L. N. Yankopoulos, N. A., Federici, E. E. and Abelmann, W. H. Hemodynamic effect of ouabain upon the hypertrophied left ventricle in aortic stenosis, J. Clin. Invest. 42:912, 1963.

2. Y kopoulos, N A Kawai, C Adler I N and Abelma n, W H Hemodynamic effect of ouabain i patient with idiopathic myocardial disease Clin Res 12 196, 1964
3 Yankopoulos, N A nd Abelmann, W H : Hemodynamic effect of digitalis, Proc New England C rdiova Soc 23:24 1965
4 Stewart H J nd C hn, A F Studies on the effect of the action of dig talis on the output of blood f om the he rt III Part 1 The effect on the output in ormal human heart Part 2. The effect on the output of heart in heart fa lure w th congestion in human beings, J Cl n I est 11:917 1932
5 Bra nwald E Blondwell, R D Goldberg, L I and Morrow A G Studies on digitalis. IV Observation in ma on the effect of digitali prepar tion on the cont ct l ty of the un-f iling heart nd on tot l v scular resist nce J Cl Invest 40:52 1961
6 Mason D T nd Braunwald E Studies on dig talis IX Effects of ouabain on the non-f iling huma heart J Clin I vest 42 1105 1963
7 Sonnenblick, E H Williams, J F J Glick G M son D T nd Braunw ld E. Studies on digitalis XV Effects of cardiac glycosides on m ocardial force-velocity elations in the nonf iling h man heart Circul tion 34:532 1966
8. Cott n, M De\ and Stopp P E Action of digitalis on the onf ling heart of the dog Am J Physiol 192 114 1958
9 Selzer A nd Malmborg R O Hemodynamic effects of digoxi latent cardiac f ilure Circulation 25:695 1962
10 Katznelson, G Jreissaty R M Levinson G E Stein S W and Abelmann W H Combined aortic and mitral stenosis, Am J Med. 29:242 1960.
11 The Criteria Comm ttee of the New York Heart Association Inc. Diseases of the heart nd blood vessels, Nomenclature and criteria for diagnosis, ed. 6 Boston 1964 Little Brown & Company
12 Hamilton W F Riley R L. Atty h A M Cournand A. Fowell, D M Himmelstein, A., Noble R P Remington, J W Richards, D W J Wheeler N C and W tham A. C. Comparison of the Fick and dy injection methods of measuring the cardiac output in man, Am J Physiol. 153:309 1948
13. Gregg D E. Shadle O W Ferguson, T B and Marzetta, L. A. An improved cuvette densitometer for cardiac output determination by the dye-dilution method Rev Scient. I trument 24:696, 1953
14 McNeely W F nd Gravallese M A. Measurement of cardiac output by dye dilution techniques Use of integrated sample collection in calibration of the photometric instrument, J Appl. Physiol. 7:55 1954
15 Murphy G W Schreiner B F Bleakley P L. and Yu, P N Left ventricular performance following digitalization in patients with and without heart failure, Circulation 30:358, 1964
16. Fisher R A Statistical methods for research workers, Hafner 1950.
17 W llace A G Skinner N S., J and Mitchell, J H Hemodynamic determinants of the maximal rat of rise of left ventricular pressure, Am J Physiol. 205:30, 1963
18. Reeves, T J Hefner L. L. Jones, W B., Cogh C Prieto, G., and Carroll, J The hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction, Am. Heart J 60 745, 1960
19 Sarnoff S J and Bergl nd, E Ventricular f nction I Starling law of the heart tudied by means of simultaneous right and left ventricular f nction curves in the dog, Circulation 9 706 1954
20. Yu, P N Schreiner B F J Cohen, J nd Murphy G. W : Idiopathic cardiomyopathy A study of left ventricular f nction nd pulmonary circulation in 15 patients, Am. Heart J 71:330, 1966.
21 Ross, J Jr Braunwald E Waldha sen, A nd Lewis, B Studies on dig talis II Extracardiac effect on venous return and on the capacity of the peripheral vascular bed, J Clin Invest 39:937 1960.
22 Daggett W M and Weisfeldt M L. Influence of the mpathetic nervous system on the response of the ormal heart t digitalis, Am J Cardiol. 16:394 1965
23. Bra nwald E Brockenbrough E. C., and Frye, R L Studies on digit lis V Comparison of the effect of ouabain of left ventricular dynamics in valvular aortic tenosis nd hypertropic subaortic stenosis, Circulation 26 166, 1962.
24 Akbarian, M Yankopoulos, N A., and Abelmann W H Hemodynamic effects of ouabain i patient with mitral stenosis nd sinus rhythm Am J Cardiol. 21:241 1968.

Effects of brachial artery catheterization on arterial pulse and blood pressure in 203 patients

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Retrograde catheterization of the aorta, the coronary arteries, and the left ventricle via brachial arteriotomy has become an accepted technique in the evaluation of congenital, valvular, and coronary heart disease. Segmental occlusion at the arteriotomy site has been reported in the literature,[1-9] however, the effects of arteriotomy on blood pressure (BP) determination by sphygmomanometers have not been stressed.

No emphasis has been placed on postarteriotomy occlusion as a major cause of absent or unequal radial pulses and BP and on the clinical implications of this complication. In order to determine the incidence of absence or inequality of the radial pulses and BP's, we have reviewed a series of 203 patients who underwent catheterization in our hospital by means of a brachial arteriotomy.

Methods and material

A transverse incision about 2 cm. long was made in the right antecubital fold in 197 patients and in the left in 6 patients. The brachial artery (BA) was dissected free for about 1.5 cm. and while being held between 2 elastic bands to prevent bleeding, it was incised transversely with pointed iris scissors. The 1 to 2 mm. incision was then spread slightly with iris forceps to facilitate entry of the catheter. No heparin was used. Before closing the incision, the BA was allowed to bleed briskly from above and below the arteriotomy site. In our first 143 patients, the arteriotomy was closed with a purse string of 5-0 silk, and in our last 60 patients, it was closed with a continuous running suture of 6-0 Tevdek.

Our study began in September, 1965, and ended in May, 1967. Letters were sent to 298 patients who underwent retrograde BA catheterization in our hospital between February, 1959, and April, 1967, asking them to return for evaluation of their pulses and BP. The 203 patients who responded were evaluated by one of us in 113 patients, by other physicians in 86, and by nurses in 4. Auscultatory BP was measured in the usual fashion with a standard cuff wrapped about the upper arm and the stethoscope placed over the BA. A difference of less than 10 mm. Hg systolic was considered to be within normal limits. The radial pulse in the catheterized arm was graded as follows: 0, no radial pulse; 1+, the radial pulse was feeble and not immediately felt; ++, the radial

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pulse was moderately diminished in comparison to the pulse in the noncatheterized arm 3+ the radial pulse was slightly diminished in comparison to the pulse in the noncatheterized arm and 4+ both radial pulses were equal and full The BA pulse was evaluated in 65 patients.

Table I indicates the time which elapsed between arterial catheterization and entry in our study The age of our patients is presented in Table II There were 101 men and 102 women A total of 94 of our patients had acquired valvular heart disease (including 30 patients with aortic stenosis) 61 had congenital heart disease 24 had coronary heart disease and there were 23 patients in the miscellaneous category

Results

In 79 of our 203 patients (38 9 per cent) the radial pulse in the catheterized arm was equal to the pulse in the other arm (4+) in 49 (24 per cent) it was 3+ in 39 (19 2 per cent) it was 2+ and in 28 (13 8 per cent) it was 1+ The radial pulse was absent by palpation in 8 patients (3 9 per cent) of the total series. The auscultatory BP in both arms was equal or differed by less than 10 mm Hg in 119 patients (59 per cent) In 84 patients (41 per cent) the catheterized arm was 10 mm. Hg or more lower than the BP in the other arm with a mean difference of 19 mm Hg and a range of 10 to 60 mm Hg

BP by auscultation could not be obtained in 57 patients (28 per cent of the total) This group comprised the 8 patients who had absent radial pulses and 49 patients whose radial pulses were graded as follows 1+ in 21 patients, 2+ in 19 and 3+ in 9 Of these 57 patients, 29 had their BA pulse evaluated 25 had no BA pulse (86 per cent) and 4 had a fair pulse (14 per cent)

An attempt was made at determining the BP by radial palpation in 22 patients without auscultatory BP The BP was equal in both arms in 6 patients and was 10 mm Hg or more lower in the catheterized arm in 16 patients with a mean difference of 21 mm Hg and a range of 10 to 50 mm Hg

BA pulses were evaluated in 65 of our patients in which 39 per cent had no BP by auscultation. In 27 of the 62 patients, the BA pulse was absent and of these 25 had no BP by auscultation and 3 showed a BP lower by 5 15 and 35 mm. Hg, respectively in the catheterized arm In the remaining 37 patients, the BA pulse was fair to good and in this group, 4 (11 per cent) had no auscultatory BP and 11 (30 per cent) had a BP in the catheterized arm lower by 10 mm. Hg or more

In the 27 patients who had no BA pulse the radial pulse was palpable in 25 patients (93 per cent) being 1+ in 8, 2+ in 11 and 3+ in 6.

Of the 143 patients whose BA was closed with a silk purse string no auscultatory BP was obtained in 46 (32 per cent) the incidence of absent BP was only 18 per cent in the 60 patients whose arteriotomy was closed with a running suture of Tevdek.

Of 108 patients in whom the duration of the arterial catheterization was one hour or less, 17 per cent had no BP by auscultation whereas in 95 patients whose arterial

Table I Interval between catheterization and entry into study

Time	No. of patients
0 to 1 mo.	15
2 to 6 mo.	37
7 to 12 mo.	24
1 to 2 yr	57
3 to 5 yr	49
6 to 7 yr	2
Total	203

Table II Age range

Age (yr.)	No. of patients
0 to 5	24
6 to 10	18
11 to 20	19
21 to 40	54
41 to 50	50
51 and over	38
Total	203

catheterization lasted more than one hour 38 per cent had no BP

Coldness and numbness of the limb was not uncommon, but they regressed within 5 days in most of our patients. Only 2 of our patients showed significant signs and symptoms of arterial insufficiency despite a 2+ radial pulse in the first and a 1+ in the second. The symptoms subsided within 5 months in the first patient but persisted in the second patient as cramps during writing 4 years after catheterization.

Discussion

The risk of arterial occlusion is always present following arterial catheterization. Fortunately, abundant collateral circulation permitting survival of the arm makes the BA ideal for retrograde catheterization and persistent arterial insufficiency is rare (1 per cent of our patients).

In our series of 203 patients, occlusion or stenosis of the BA associated with unobtainable sphygmomanometric BP by auscultation occurred in 57 patients (28 per cent). Of these 57 patients, 8 (3.9 per cent of the total series) had no radial pulse in the catheterized arm. In 43 per cent of our patients the radial pulse was significantly diminished and in 41 per cent the BP was significantly decreased in comparison to the noncatheterized arm.

A review of the literature fails to demonstrate a study similar to ours involving the determination and quantitation of both the BP and the radial pulse and a long term follow up. Sones, who closed his brachial arteriotomy with a mattress suture of 5-0 Tevdek indicated that "segmental occlusion at the site of arteriotomy has occurred in 6 to 7 per cent of the patients undergoing selective coronary arteriotomy. No information is available on the BP in these patients. If an absent radial pulse was used by Sones as evidence of arterial occlusion his percentage would compare to our figure of 3.9 per cent with absent radial pulses however since in our series the radial pulses were felt in 96 per cent of patients with absent BA pulses, a large number of BA occlusion could have been missed by Sones. Even if he used BA pulses it should be realized as demonstrated in our study that 11 per cent of the patients with fair to good BA pulses had no BP obtainable by auscultation.

In Vlad and associates series of 500 infants and children loss or diminution of peripheral pulsations has been noted in about one-third of the patients repair of the vessel was performed by a purse string suture or a continuous running suture with 6-0 mersilene. Voci and Hamer who repaired the BA with a continuous silk suture, reported that about one-third of 80 patients studied had absent peripheral pulses following arteriotomy. Sewell[1] reported that the radial pulse was lost in 2 of 8 patients that had brachial arteriotomy closed with a mattress suture of silk in one of 23 closed with mersilene and in none of 119 closed with Tevdek. No information is available on BP in any of the above series and in none were the pulses graded. Aguilar and colleagues, in their follow up study of 137 patients who underwent arterial catheterization stated briefly that "normal results including a normal BP and pulse excursion in the limb used for catheterization were obtained in all but 3 patients.

Considering the large number of patients undergoing BA catheterization for evaluation of rheumatic heart disease congenital heart disease and particularly for selective coronary arteriography it becomes evident that arterial occlusion following brachial arteriotomy has become a major cause of absence and inequality of BP and radial pulses. Despite its importance arterial catheterization is not mentioned in the literature as the cause of absent or unequal pulses and BP's. The scar of a previous catheterization should be sought in the antecubital fossa and its presence should suggest the possibility of finding unequal or absent BP and pulses. An awareness of this complication of arteriotomy is of prime importance to the physician or nurse evaluating the BP or pulses in patients who have undergone BA catheterization. Failure to appreciate that absent or low cuff pressures in these patients does not necessarily indicate arterial hypotension may lead to dangerous errors in diagnosis and therapy particularly in shock. Treatment with vasopressors because of the false impres-

sion of hypotension may have disastrous effects. The noncatheterized arm should be used for BP and pulse evaluation unless equality between the BP and pulses in both arms can be established.

In patients who underwent BA catheterization, the diagnosis of subclavian steal syndrome or the evaluation of subclavian artery patency before internal mammary implantation should be based on axillary pulses, not on BA and radial pulses and BP in the arms.

Repeated arterial catheterization for evaluation of coronary artery disease and revascularization procedures and for the study of valvular prosthesis and their complications is not uncommon. In coronary heart disease, the right BA is usually used for coronary arteriography, and the left BA is required for opacification of the left internal mammary implant. It should be realized that in patients who have no pulses and no BP or a low BP in a catheterized arm, a second arterial catheterization via the other BA would run a 28 per cent risk of rendering impossible clinical determination of the BP in the upper extremities. In coarctation of the aorta, occlusion of the second BA would result in the impossibility to determine clinically the precoarctation BP. It would be preferable in cases of previous BA occlusion to utilize the percutaneous femoral approach, which is not, however, suitable for selective internal mammary catheterization, or to forgo a repeated arterial catheterization unless it is absolutely indicated.

Those patients who have had no obtainable BP by auscultation have either complete occlusion of the BA or significant stenosis resulting in low flow through the BA segment. Rodbard[8] and Cohn[9] have stressed the role of blood flow in determining the intensity of the Korotkoff sounds. In our patients who had no BA pulses and no obtainable BP by the auscultatory method, the presence of satisfactory collateral circulation is probably responsible for the presence of a radial pulse, albeit diminished, and of a BP obtainable by radial palpation. We postulate that absent or relatively low auscultatory BP is due to one of 3 mechanisms: a total BA occlusion with no BA or radial pulses, a total BA occlusion with absent BA pulses, palpable radial pulses and blood pressures via collateral circulation, or stenosis of the BA with weak or diminished pulses because of restricted BA flow.

The length of the arterial catheterization was an important factor in the incidence of BA occlusion in our series. Our study was not intended to compare the various techniques of arterial closure; however, in our series the incidence of BA occlusion when a silk purse string was used was higher than it was with a running suture of Tevdek.

We would like to urge meticulous and quantitative follow-up of BA and radial pulses and BP by auscultatory and palpatory methods by other groups in order to determine the extent of the BA occlusion problem following arteriotomy. Evaluation of radial pulses alone does not rule out BA occlusion because of the extensive collateral circulation. Evaluation of the BA pulse or the auscultatory BP which corresponds closely to the status of BA pulses are more indicative of BA occlusion.

Summary

We have reviewed a series of 203 patients who underwent retrograde cardiac catheterization by means of brachial arteriotomy. Occlusion or stenosis of the brachial artery (BA) associated with unobtainable auscultatory blood pressure (BP) occurred in 57 patients (28 per cent). Of these 57 patients, 8 (3.9 per cent of the total series) had no radial pulse. Brachial arteriotomy has become a major cause of absence and inequality of BP and radial pulses. Failure to appreciate this fact may lead to dangerous errors in diagnosis and therapy, particularly in shock.

We would like to acknowledge the assistance of Miss Rose Mary Solomson in analyzing our data. The following physicians participated in the project: Drs. Robert J. Hussar, Barbar Witter, Richard Faulkes, James O'Brien, and Bimelin Lahiri.

REFERENCES

1. Vlad, P., Hohn, A., and Lambert, E. C.: Retrograde arterial catheterization of the left heart. Experience with 500 infants and children, Circulation 23:787, 1961.
2. Aguilar, S., Kalbfleisch, M. G., and Hugenholtz, P. G.: Retrograde arterial catheterization of the left ventricle in 388 patients, New England J. Med. 274:312, 1966.
3. Sones, F. M., Jr., Hurst, J. W., and Logue, R. B.

editors The heart, New York, 1966, The Blakiston Division, McGraw Hill Book Company

4. Voci, G., and Hamer, N. A. J. Retrograde arterial catheterization of the left ventricle, Am. J. Cardiol. 5:493, 1960.
5. Toole, J. F. and Tulloch, E. F. Bilateral simultaneous sphygmomanometry. A new diagnostic test for subclavian steal syndrome, Circulation 33:952, 1966.
6. Bell, J. W. Treatment of post-catheterization arterial injuries, Ann. Surg. 155:591, 1962.
7. Fowler, N. O. Examination of the heart, Part II Inspection and palpation of venous and arterial pulses, American Heart Association New York, 1963.
8. Rodbard, S. The significance of the intermediate korotkoff sounds, Circulation 8:600, 1963.
9. Cohn, J. N. Blood pressure measurement in shock, J.A.M.A. 199:972, 1967.
10. Sewell, W. H. Coronary arteriography by the Sones technique. Technical considerations, Am. J. Roentgenol. 95:673, 1965.

The anatomic basis of the electrocardiographic abnormality in incomplete left bundle branch block

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Since the introduction of unipolar electrocardiography, the anatomic basis of bundle branch block (BBB) has been studied by Sanabria,[1,2] Langeron and colleagues, Lenègre, Lev and Unger and their associates,[3-5] Lev,[7] Rossi,[8] Segers, and Glomset and co-workers.[9-11] Langeron and colleagues[3] and Lev and Unger and their associates[4,5] have felt that this electrocardiographic abnormality has a basis in lesions of the conduction system, and such correlation was especially stressed by the monumental work of Lenègre.[4] However, such correlation was doubted by Sanabria,[1,2] Segers,[9] Glomset and co-workers,[10,11] and Rossi. Among those who have favored this correlation, the problem of the pathogenesis of left bundle branch (LBB) lesions in coronary disease has arisen. According to Lenègre, the lesions seen in this disease are of a mechanical rather than an ischemic nature.

The purpose of this report is therefore twofold: (1) to investigate further the correlation of the electrocardiographic findings and conduction system lesions in incomplete left bundle branch block (LBBB) and (2) to shed some light on the pathogenesis of LBB lesions in coronary disease.

As to the electrocardiographic diagnosis of incomplete LBBB, four criteria have been advanced for such a diagnosis: (1) a QRS interval of 0.10 to 0.12 second;[illegible] (2) prolongation of the time of the intrinsicoid deflection to 0.06 second or greater in the left precordial leads;[illegible] (3) absence of a Q wave in the left precordial leads;[illegible] (4) notching and/or slurring of the ascending limb of the R wave in the left precordial leads.[illegible] However, any single one of these criteria taken by itself is considered to be invalid since it can be found in normals and in other abnormalities.[illegible]

Materials and methods

Four cases, in which clinically a diagnosis of incomplete LBBB was made, were investigated by means of serial sectioning of the conduction system and pathological study of the entire heart. A diagnosis of incomplete LBBB was made using the criteria previously enumerated.

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The method of histological study of the heart was as follows

The sinoatrial (S-A) node was serially sectioned and every twentieth section was retained The atrioventricular (A V) node, bundle, and the beginning of the bundle branches were serially sectioned and every tenth section was retained The remainder of the bundle branches up to the region of the moderator band were serially sectioned and every twentieth section was retained The remainder of the heart was completely cut into blocks and two sections were taken from each block Alternate sections were stained with hematoxylin-eosin and Weigert van Gieson stains. In this manner 1 778 1 198 2 049 and 1,387 sections were studied from Cases 1 to 4 respectively

Findings

The pathological findings excluding those of the conduction system are found in Table I (Fig 1)

Case 1 CLINICAL REVIEW L. S., 68 year-old man had three admissions to the hospital prior to his terminal admission. His initial admission was on April 29 1955 with diagnosis of arteriosclerotic heart disease, atrial fibrillation, and cerebral embolism. There was a previous history of two myocardial infarctions, the last one in 1953 The heart, upon examination, showed atrial fibrillation with ventricular rate of 84 with no murmurs present. The patient was discharged three days after admission with no residuals.

He was readmitted on Aug 9 1955 in acute pulmonary edema. The heart was clinically enlarged to the left, and atrial fibrillation with ventricular rate of 124 was present. The blood pressure was 132/90 Rapid recovery ensued after treatment with digitalis, diuretics, sodium restriction, and a right thoracentesis.

The final admission occurred on April 1 1956 with the patient in acute pulmonary edema. He died 9 hours after admission following convulsive seizure.

ELECTROCARDIOGRAPHIC ANALYSIS. On Aug 11 1955 features noted were atrial tachycardia with variable conduction and ventricular premature contractions Inferior wall and anteroseptal myocardial infarction QRS 0.10 with intrinsicoid deflection of 0.06 sec. in the left precordial leads Q absent in L, aV L, and left precordial leads R notched and slurred.

On Aug 15 1955 (Fig 2), findings included normal sinus rhythm with occasional ventricular premature contractions P R interval 0.18 sec. QRS 0 11 sec. with intrinsicoid deflection of 0.07 sec. in the left precordial leads. Q was absent in L aV L, and left precordial leads with slurring and notching of the R.

CONDUCTION SYSTEM. S-A node A fine infiltration

Table I Pathological findings in the heart

	Case 1	*Case 2*	*Case 3*	*Case 4*
Weight of heart (grams)	480	400	450	500
Coronary arteries	Complete obliteration of anterior descending and marked narrowing of right and left circumflex arteries	Almost complete occlusion of right main and left circumflex arteries	Complete occlusion of anterior descending and left circumflex. Marked narrowing of right coronary	Complete occlusion of anterior descending, and narrowing of left and right circumflex
Hypertrophy and enlargement	Right ventricular hypertrophy Left ventricular hypertrophy and enlargement	Hypertrophy and enlargement of both ventricles	Hypertrophy of both right and left ventricles	Hypertrophy of both right and left ventricles
Microscopic examination	Old subendocardial infarct of septal and parietal walls of left ventricle. Early acute infarct of septum. Summit of ventricular septum involved in old infarct	Recent organizing, and old infarct of anterior and septal walls and old infarct of posterior wall of left ventricle Recent, organizing, and old infarct in summit of ventricular septum	Recent, organizing and old infarct of anterior posterior and septal walls of left ventricle with involvement of the summit in old infarct	Recent and old infarct of septal and parietal walls of left ventricle with involvement of summit in old infarct (Fig 1)

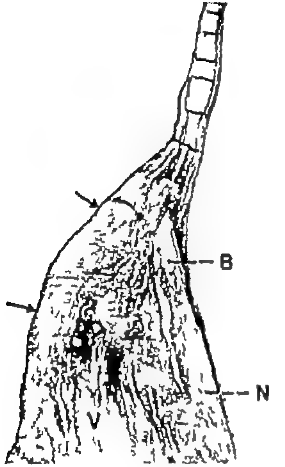

Fig. 1. Section through summit of the ventricular septum (Case 4). (Weigert-van Gieson stain, ×9.) *V*, ventricular myocardium; *N*, A-V node; *B*, penetrating portion of A-V bundle, and arrows point to the fibrosis of the summit and the central fibrous body.

of mononuclear cells was present in the head. Focally there was acute degeneration of cells. Some of the arterioles were thickened and narrowed. Approaches to the S-A node: There was an acute degeneration of cells with slight fibrosis, fine infiltration of mononuclear cells and small zones of hemorrhage focally. Approaches to the A-V node: Focal acute degeneration of muscle cells with occasional zones of mononuclear cell infiltration were present. A-V node: There was focal acute degeneration of fibers. The branches of the ramus septi fibrosi were sclerotic, the nodal branch was narrowed, and the arterioles were thickened and narrowed. A-V bundle penetrating portion: There was focal acute degeneration of individual cells with focal fine elastosis. A-V bundle branching portion: Hemorrhage was present here as well as fine elastosis and a focal infiltration of mononuclear cells. Bifurcation: This was the seat of marked fatty infiltration with fibrotic replacement of the left side.

LBB. A disruptive fibroelastic lesion was present at the junction of the fibers of the posterior part of the main LBB with the A-V bundle with hemorrhage in these fibers and an infiltration of mononuclear cells (Fig. 3). The cells of LBB distal to the disruption were small but further down resembled Purkinje cells. The fibers of the anterior part of the left main bundle likewise showed marked fibrosis. Further down only scattered fibers of LBB remained which showed degenerative changes in fibrosis and infiltration of mononuclear cells.

RIGHT BUNDLE BRANCH (RBB). The first part of RBB showed hemorrhage with slight infiltration of mononuclear cells. The second part showed only acute degeneration. The third part was the seat of fatty infiltration with acute degeneration of cells, but no interruption in continuity.

Case 2. CLINICAL REVIEW. H. F., 70-year-old man, was admitted to the hospital on Feb. 9, 1956, with a history of onset of precordial distress one week prior to admission with recurrent shortness of breath. On the day of admission he had severe chest pain with the immediate development of shock and failure with no response to treatment, and he died 1 hour after admission.

ELECTROCARDIOGRAPHIC ANALYSIS. On Feb. 9, 1956 (Fig. 4), the following data were obtained: Variable focus mechanisms ranging from sinus tachycardia to normal sinus rhythm; A-V dissociation in Leads V, V, and V. The P-R interval was 0.16 sec.; QRS 0.12 sec. with intrinsicoid deflection of 0.04 sec.; Q absent in L, V, V, and V; slurring of upstroke of R; acute inferior wall infarction.

CONDUCTION SYSTEM. S-A node: There were no changes. Approaches to the S-A node: Slight fibrosis, acute degeneration of cells, arteriolosclerosis, and fatty infiltration were present. Approaches to the A-V node: There was fibrosis, with focal acute degeneration of cells. A-V node: Noted were fibroelastosis, focal irregularity of staining of cells, an occasional infiltration of mononuclear cells, and a slight narrowing of the nodal branch of the ramus septi fibrosi. A-V bundle, penetrating portion: There was distinct fibrosis with focal irregularity of staining of cells. A-V bundle branching portion: The fibrosis and elastosis were more marked with focal irregularity of staining of cells. Bifurcation: There was considerable fibrosis.

LBB. Fibers of the posterior part of the left main bundle showed marked replacement by fatty tissue with some fibrosis (Fig. 5). The remaining cells were small in size and irregularly stained. The process of fatty replacement became even more accentuated in the anterior part of the bundle and its ramifications, with just a few strands of bundle remaining. The peripheral Purkinje cells on the left side were about the same size, or perhaps somewhat smaller than myocardial cells.

RBB. The first part showed slight fibroelastosis with acute degeneration of cells. Close to the end of the first portion the bundle was surrounded by fat with slight fibrosis. Some of the cells stained irregularly. The third portion was not present on the specimen.

Case 3. CLINICAL REVIEW. H. J., 68-year-old Caucasian woman, was admitted to the hospital on Dec. 16, 1955, with a history of recurrent bilateral shoulder and interscapular pain for 24 hours prior to admission.

Her past history included a severe febrile urinary

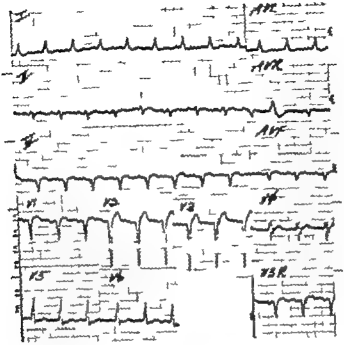

Fig. 8 ECG taken on Aug. 15, 1955 (Case 1)

tract infection 10 years prior to admission with no known recurrence, hypertension of unknown duration and previous myocardial infarction. Increasing dyspnea upon exertion over the course of several years occurred with recurrent pulmonary congestion treated by periodic mercurial diuretics, sodium restriction and digitalis. The latter had been stopped one month prior to admission.

Upon admission the patient was acutely ill and cyanotic. The heart was diffusely enlarged to the left and no murmurs were noted. The rhythm was irregular, the blood pressure was 120/70 and the lungs were clear. The clinical course was characterized by recurrent substernal shoulder and arm pain. Fever rose to 101° and remained there throughout her course. Nonprotein nitrogen (NPN) was 69 mg. per cent, creatinine 2.3 mg. per cent. Treatment was supportive and symptomatic in addition to anticoagulants, mercurial diuretics and antibiotics. The patient died suddenly on Dec. 15, 1955 while eating, nine days after admission.

ELECTROCARDIOGRAPHIC FINDINGS. On Dec. 19, 1955 (Fig. 6), the following readings were obtained: atrial fibrillation with ventricular premature contractions multifocal, single and repetitive—(■ in V and V) QRS 0.08 sec. Q absent I, L, V, V and V, intrinsicoid deflection 0.06 sec. antero-septal myocardial infarction.

On Dec. 23, 1955 there were no major changes.

CONDUCTION SYSTEM. S-A node: Marked arteriolosclerosis was present throughout. There was hemorrhage and mononuclear cell infiltration in the periphery of the head of the node with some involvement of the node. Approaches to the S-A node: Considerable arteriolosclerosis was present. Fibrous and fatty infiltration were in evidence. Approaches to the A-V node: Focal fibrosis with marked fatty infiltration were present. On the periphery of the node there was fine mononuclear cell infiltration. The annulus septi fibrosi was somewhat thickened. A-V node: Fatty infiltration with fine fibrosis were present with slight fibrosis. Marked arteriolosclerosis with narrowing were in evidence throughout. A-V bundle, penetrating portion: Fibrosis of the left side of the bundle lay adjacent to calcification on the left side of the summit of the septum. A-V bundle, branching portion: There was fibrosis with focal hemorrhage. Bifurcation: Fibrous and fat infiltration were in evidence.

LB: A calcific lesion was present in the septum adjacent to the origin of LBB. The fibers of the posterior part of the main LBB consisted of small cells, surrounded by mononuclear cells (Fig. 7). Many cells were replaced by fatty tissue with elastosis and fibrosis (Fig. 8). The fibers of the anterior part of the main left bundle showed marked fibrosis with only remnants remaining. Further distally there was marked fatty replacement with some fibrosis. The peripheral Purkinje cells were slender and did not stain like Purkinje cells. Recent hemorrhage was present more anteriorly.

RB: The first part showed slight increase in the connective tissue with focal irregularity in staining of cells. The second portion showed the same acute degeneration as it passes through an infarct. The third part showed moderate fibrosis together with slight infiltration of mononuclear cells and hemorrhage.

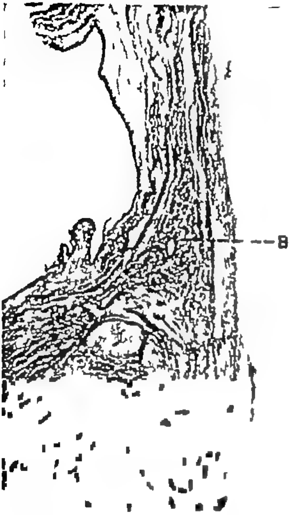

Fig. 3. Section through branching portion of A-V bundle and some fasciculi of LBB showing fibroelastic replacement of LBB (Case 1). (Weigert-van Gieson stain ×35.) B bundle. V ventricular musculature and arrow points to LBB.

Case 4. CLINICAL REVIEW. J. E., 67-year-old Caucasian man was admitted to the hospital on Dec. 27 1955 with history of sudden onset of crushing chest pain with the immediate development of shock and left ventricular failure. Despite the use of O_2, vasoconstrictors, opiates, and supportive therapy shock persisted and the patient died 2 hours after admission. No previous history was obtainable.

ELECTROCARDIOGRAPHIC ANALYSIS. On Dec. 27 1955 (Fig. 9) the results found were normal sinus rhythm with ventricular premature contractions. QRS 0.10 sec. with slurring and notching of the R in the left precordial leads. Q absent in L, aV$_L$ and left precordial leads. Intrinsicoid deflection 0.06 sec. P-R interval 0.18 sec. premature atrial contraction in L. ST segment depression in V... Inferior septal and anterior wall infarctions.

CONDUCTION SYSTEM. S-A node: Focally there was an irregularity of staining of muscle cells. Approaches to S-A node. Marked fatty infiltration with marked focal irregularity of staining of cells were present. An occasional arteriole was thickened. Approaches to A-V node. Irregularity of staining of muscle cells, focal fibrosis, and elastosis were present. The small coronary arteries were thickened and narrowed. The nodal branches of the ramus septi fibrosi showed marked thickening and narrowing. A-V node: The beginning of the node showed distinct fine elastosis. The cytoplasm of the cells of the A-V node was irregularly stained and focal infiltration of mononuclear cells was present. The central fibrous body and the annulus of the mitral valve were thickened. A-V bundle penetrating portion. Irregular stainability of cells with an occasional infiltration of mononuclear cells was present. Various spots showed fine elastosis with focal fibrosis. A-V bundle branching portion. There was marked elastosis with focal fibrosis. At the origin of the posterior radiation of the LBB there was a large focal area of fibroelastosis replacing the bundle in which the fibroelastic fibers were arranged in whorls (Fig. 10). This area was focally infiltrated with macrophages. Scattered degenerated muscle cells remained in this area. Hyaline masses were also seen. Elsewhere the bundle showed marked elastosis with focal fibrosis and vacuolar degeneration of the muscle cells. Bifurcation. There was considerable elastosis.

LBB. The fibers of the posterior part of the main left bundle were completely cut off from the branching bundle by a fibroelastic lesion. In this area, there were linear formations stained yellow with van Gieson. These may be degenerated or mummified cells. Distal to this point, degenerating Purkinje cells were present. Further distally the cells which should be Purkinje cells were small. The fibers of the anterior part of the left main bundle were present, but were small and degenerated. They were smaller than the myocardial fibers, although they should be Purkinje cells. More distally they took on the appearance of Purkinje cells. Here there was fat tissue replacement of the LBB. Occasional foci of small fibers were seen here, and there was slight infiltration of mononuclear cells. The periphery of the LBB showed irregularity of staining as it lay in an early acute infarct. Some parts of the periphery of LBB were encased in connective tissue.

RBB. The first part showed elastosis with slight fibrosis. This continued into the second portion but in addition there was increased eosinophilia of fibers and occasional pyknotic nuclei. The third part of RBB showed fatty infiltration, irregularity of the staining of cells, with a slight infiltration of mononuclear cells.

Discussion

In our four cases of incomplete LBBB we are confronted with old and recent lesions in the conduction system. The old lesions in three cases consist of a fibroelastic replacement of the part of the junction of the A-V bundle with the LBB with atrophy of remaining cells of this junction and atrophy of the more distal cells of the LBB or replacement by fat tissue. In the fourth case there is a more diffuse

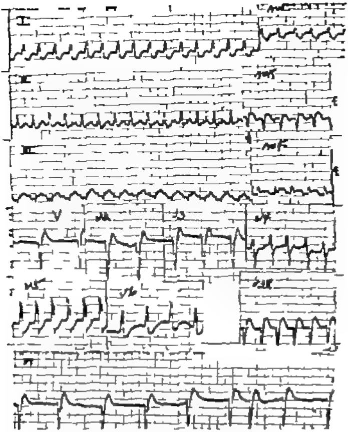

Fig 4 A ECG taken on Feb 9 1956. B Strip of V in the same ECG showing A V dissociation (Case 2).

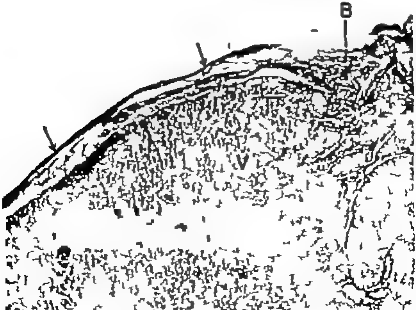

Fig 5 Section through branching portion of A V bundle and some fasciculi of LBB showing fibrosis of the A V bundle and partial replacement of LBB by fat tissue (Case 2). (Elastic-van Gieson stain ×21) B A V bundle; V ventricular myocardium; and arrows point to LBB.

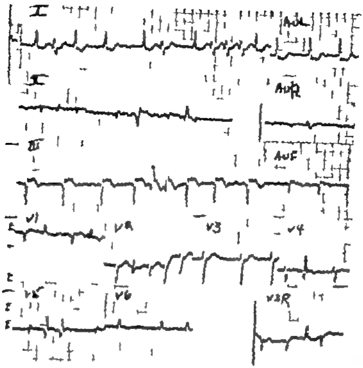

Fig 6 ECG taken on Dec. 19 1955 (Case 3).

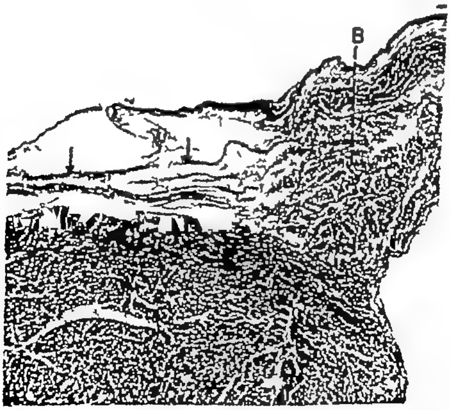

Fig 7 Case 3 Section through branching portion of the A V bundle and some fasciculi of LBB showing conversion of LBB int small cells (trophy) (Case 3) (Weigert van Gieson stol ×41) *B* A V bundle *V* ventricular myocardium and arrow point to LBB

Fig. 8. Section through fasciculi of LBB more distally showing partial replacement by f t tissue (Case 3). (Weigert-van Gieson stain ×22.) V entricular myocardium; and arrows point to LBB

similar lesion without emphasis on the junction. The recent lesions consist of focal irregularity of staining of the cytoplasm of some of the cells throughout the con duction system

In two cases, the lectrocardiogram (ECG) in view of its t ming should be correlated with the old lesions only while in two cases it should be correlated with old and recent lesions. In view of the minimal nature and focality of the recent lesions in any one area and their diffuse distribution in the conduction system we believe them to be of little importance in the correlation of LBBB. Thus, the correlation in all four cases is made with the old lesions.

These lesions are better understood by a knowledge of the anatomy and blood supply of the LBB. The fibers of the LBB are given off in a steady fine stream of fasciculi

as the A-V bundle emerges from the central fibrous body and enters the lower confines of the pars membranacea until the bifurcation into the RBB and the remaining fibers of the LBB is reached. These fibers of the LBB lie below the posterior aortic cusp and comprise a fairly wide structure as compared to the RBB. They proceed distally in a parallel fashion for a varying distance and then segregate themselves into anterior and posterior radiations which proceed to the anterior and posterior papillary muscles and the surrounding septal areas respectively, eventually forming nets of Purkinje cells.

The blood supply to the main LBB[11] is by way of the terminal portion of the ramus septi fibrosi, the ramus septi ventriculorum superior, and the ramus cristae—all of which are derived from the right coronary artery, reinforced by some small branches from the anterior descending. The anterior perforating branches from the anterior descending supply blood to the anterior radiation while the posterior perforating branches coming from the posterior descending furnish blood to the posterior radiation. The peripheral portion of the Purkinje cells are supplied by the blood nourishing the surrounding myocardium.

The LBB can thus be seen to be especially vulnerable to injury in its main (beginning) portion. Here it emerges from the end of the central fibrous body and from the confines of the *pars membranacea in fine filets* which may be subject to the mechanical injury inflicted by the changes in the left side of the fibrous skeleton of the heart. Likewise, it is sufficiently compact, as compared to its more distal ramifications, to be subject to destruction by ischemia. Ischemic lesions of the main left bundle are most apt to be found when both the anterior descending and right main coronary

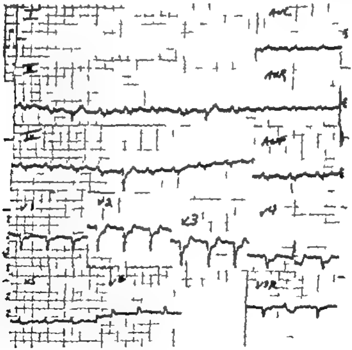

Fig. 9. ECG taken on Dec. 27, 1955 (Case 4).

Fig. 10. Section through branching portion of the A-V bundle and some fasciculi of LBB showing marked fibrosis of the A-V bundle at its junction with LBB, and almost complete replacement of LBB by fibroelastic tissue (Case 4). (Weigert van Gieson stain. *A*, ×29. *B*, Enlargement of junctional area ×230.) *B*, Right side of the A-V bundle, relatively intact. *B*$_2$, left side of the A-V bundle showing disruption of architecture with scattered bundle cells, ghosts of cells, fibrosis, and focal elastosis. *LB*, remnant of LBB. *V*, ventricular septal myocardium, and arrows in *B* point to remnant of LBB.

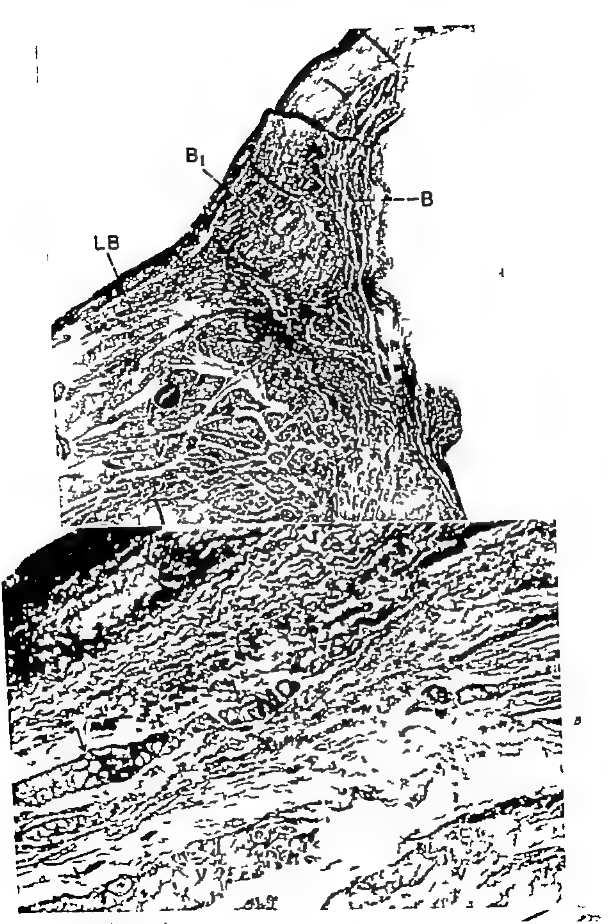

Fig. 10 For legend see opposite page.

arteries are involved although it is conceivable that occlusive disease of the right main coronary artery alone may produce such lesions

In three of our four cases there is occlusive disease of both the right main and anterior descending coronary arteries. In one however the right main was mostly involved This lends credence to the belief that the old lesions in the LBB in our case have an ischemic component in their pathogenesis.

At the same time it may be noted that in all four cases there is considerable fibrosis and sclerosis of the summit of the ventricular septum This may have occurred spontaneously since our patients are in the old age group However we are struck by the fact that the old infarct present occupies the area of the summit of the ventricular septum in all cases. We may therefore postulate that there is a component of fibrosis and weakness imparted to the summit by the ischemic process in our cases

If this is so we may be dealing with an ischemic process which acts directly upon the LBB as well as indirectly by accelerating the sclerosis of the left side of the cardiac skeleton which mechanically injures the LBB Thus are engrafted the mechanical lesions of Lenègre[4] on the basic ischemic lesions to explain the nature of the old lesions in our cases.

The pathological change of fat tissue replacement of parts of the LBB seen in all of our cases is not clearly understood today Conventionally fat tissue is considered to infiltrate parenchyma thereby producing atrophy and destruction If our interpretation is correct the reverse may be true Atrophy or destruction of cells produced by ischemia or mechanical injury may result in replacement by fat tissue.

The atrophy of Purkinje cells has been noticed previously by one of us (M L.) Its exact pathogenesis is not clear It may play a role in the slowing of conduction along the left pathway

Our four cases clearly show a correlation between the electrocardiographic abnormality incomplete LBBB and significant lesions in the LBB These lesions are considered incomplete. However it must be pointed out that in a structure as broad as the LBB a statement of completeness or incompleteness of lesions is very difficult if not impossible to make Furthermore this decision of completeness versus incompleteness must not be correlated with the electrocardiographic abnormality complete versus incomplete LBBB since the functional component cannot be completely equated with the structural component of the conduction system

Old lesions of the S-A and A V nodes were either minimal or absent in our cases. However old lesions of the left side of the A V bundle and bifurcation were prominent in two cases, and may be considered as part of the junctional lesions of LBB The diffuse fibrosis of the A V bundle in one case is probably unrelated to the LBBB The RBB in three cases showed minimal or insignificant old lesions. In the fourth case its involvement was much less than that of LBB

As concerns the ECG criteria for the diagnosis of partial LBBB these cases had the following features. (1) Q was absent in L_1 aV$_L$ and the left precordial leads in all (2) slurring or notching of R was present in all (3) QRS duration ranged from 0 08 to 0 12 sec being 0 10 to 0 12 sec in three and 0 08 sec in one and (4) the intrinsicoid deflection was 0 06 to 0 07 sec in three cases and 0 04 sec in one case In the latter case the duration of the QRS deflection was curiously the longest Thus, two cases had all four criteria for the diagnosis of incomplete LBBB and two showed three. Thus the lesions found in the LBB in our cases and hence the block were associated in any individual case with at least three of the ECG criteria It would thus appear that it is the association of criteria which warrants the ECG diagnosis of incomplete LBBB and not any one criterion This is especially so when one recalls that any *one* of the criteria alone may be found in the normal or in other abnormalities[17 - 20]

Finally it must be pointed out that in our manner of sectioning the *main left* branch and the upper parts of the radiations are serially sectioned while the *remainder* of the LBB is sampled by cutting the myocardium of that region *completely* into blocks. Thus definitive statements can be made of the main left bundle and *part* of the radiations, but *not* of the *peripheral* fine networks of the LBB Thus, a wide

spread lesion of the periphery of LBB might be related to LBBB and would not be properly evaluated in our manner of sectioning. This might explain some of the lack of correlation obtained in the literature in isolated cases of LBBB.

Summary

The hearts of four cases with coronary disease which electrocardiographically had incomplete LBBB were studied pathologically. The electrocardiographic diagnosis was based on the presence of at least three of four criteria. The pathological studies included comprehensive studies of the conduction system and the entire myocardium.

This study revealed that there was close correlation of the assumed block with lesions of the LBB. These lesions are considered to be due to both direct ischemia of the LBB and to fibrosis of the summit of the ventricular septum mechanically injuring the LBB.

REFERENCES

1. Sanabria, T.: Contribution à l'étude anatomoclinique de bloc de branche, Acta cardiol. 5:527, 1950.
2. Sanabria, T.: Étude anatomo-pathologique du bloc de branche. Rapports entre l'image électrocardiographique et l'aspect microscopique du système de His-Tawara, Acta cardiol. 8:145, 1953.
3. Langeron, L., Giard, P., and Destombes, A.: Considérations sur un bloc de branche gauche. Observation anatomo-clinique, Arch. mal. coeur 43:1107, 1950.
4. Lenègre, J.: Contribution à l'étude des Blocs de branche, Paris, 1958, J. B. Baillière et fils.
5. Lev, M., Unger, P. N., Lesser, M. E., and Pick, A.: Pathology of the conduction system in acquired heart disease. Complete right bundle branch block, Am. Heart J. 61:593, 1961.
6. Unger, P. N., Lesser, M. E., Kugel, V. H., and Lev, M.: The concept of "Masquerading" bundle branch block. An electrocardiographic pathologic correlation, Circulation 17:397, 1958.
7. Lev, M.: Complete left bundle branch block. A physiologic-pathologic correlation. Report of case, Am. Heart J. 61:149, 1961.
8. Rossi, L.: Atrioventricular conduction system and nerves in the human heart, Sc. Med. ital. (Series 2) 3:514, 1955.
9. Segers, M.: Nouvelles bases d'interprétation de l'electrocardiogram normal et pathologique, Acta cardiol. (Suppl. IV) 1948.
10. Glomset, D. J., Glomset, A. T. A., and Birge, R. F.: A morphologic study of the cardiac conduction system. Part III. Bundle branch block, Am. Heart J. 28:348, 1944.
11. Glomset, D. J., and Birge, R. F.: A morphologic study of the cardiac conduction system. V. The pathogenesis of heart block and bundle branch block, Arch. Path. 45:135, 1948.
12. Bryant, J. M.: Advances in electrocardiography. I. Intraventricular conduction, New York, 1958, Grune & Stratton, Inc., p. 117.
13. Oppenheimer, B. S., and Rothschild, M. A.: Abnormalities in the QRS group of the electrocardiogram associated with myocardial involvement (Preliminary report), Proc. Soc. Exper. Biol. & Med. 14:57, 1916.
14. Willius, F. A.: Arborization block, Arch. Int. Med. 23:431, 1919.
15. Lewis, T.: Clinical electrocardiography, London, 1913, Shaw & Sons, Ltd., p. 32.
16. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic changes associated with myocardial involvement, J.A.M.A. 69:429, 1917.
17. Carter, E. P.: Clinical observations in defective conduction in the branches of the auriculoventricular bundle, Arch. Int. Med. 13:803, 1914.
18. Wilson, F. N., and Herrmann, G. R.: Bundle branch block and arborization block, Arch. Int. Med. 26:153, 1920.
19. Kossmann, C. E.: The normal electrocardiogram, Circulation 8:920, 1953.
20. Rothberger, C. J., and Winterberg, H.: Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens, Ztschr. ges. exper. Med. 5:264, 1917.
21. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Advances in internal medicine, Vol. 2, No. 1, New York, 1947, Interscience Publishers, Inc.
22. Kossmann, C. E., Burchell, H. B., Pruitt, R. D., and Scott, R. C.: The electrocardiogram in ventricular hypertrophy and bundle-branch block, panel discussion, Circulation 26:1337, 1962.
23. Kossmann, C. E.: Advances in electrocardiography. Part III. Spread of excitation and of recovery, normal and abnormal, New York, 1958, Grune & Stratton, Inc., p. 103.
24. Sodi-Pallares, D., and Calder, R. M.: New bases of electrocardiography, St. Louis, 1956, The C. V. Mosby Company.
25. Sodi-Pallares, D., Estandía, A., Soberón, J., and Rodríguez, M. I.: The left intraventricular potential of the human heart. II. Criteria for diagnosis of incomplete bundle-branch block, Am. Heart J. 40:655, 1950.
26. Reynolds, E. W., Jr., Muller, B. F., Anderson, G. J., and Muller, B. T.: High-frequency components in the electrocardiogram, Circulation 35:195, 1967.
27. Leighton, R. F., Ryan, J. M., Goodwin, R. S., Wooley, C. F., and Wissler, A. M.: Incomplete left bundle branch-block, Circulation 36:261, 1967.
28. Sand, S. I., McLaughlin, H. M., and Bryant, J. M.: Diagnosis of incomplete left bundle branch-block, Circulation 14:994, 1956.
29. Lascano, E. F.: Irrigación normal del nódulo de Tawara, haz de His y sus ramas, Rev. argent. cardiol. 10:23, 1943.

Isovolumetric contraction period of the left ventricle

Results in a normal series and comparison of methods of calculation by atraumatic techniques

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The heart is a muscular container in which changes in length and tension are associated with cyclic changes in the volume and pressure of its contents. Ventricular systole begins by setting up of tension and ends with completion of ejection. Initially, left ventricular wall tension is translated into movement and then to rising intracavitary pressure without change in volume. This period of isovolumetric contraction (IVCT) ends when intraventricular pressure exceeds aortic pressure; the resulting gradient opens the aortic valve and ejection of blood into the aorta quickly reduces ventricular volume.

The significance of the IVCT can be summarized as follows: (1) IVCT is a direct expression of the sum of factors comprising "contractility," especially the rate of rise of left ventricular pressure (dp/dt), i.e., the speed with which ventricular muscle can compress the blood to the ejection point; (2) IVCT reflects end-diastolic stretch and secondarily end-diastolic volume; and (3) changes in IVCT reflect changes in electric, neural, metabolic, and pharmacological influences as well as anatomic disruptions of the contractile elements.

Because of its evident physiological importance, it would be desirable to have reliable methods of measuring IVCT in human beings which could also be repeated indefinitely without discomfort or danger. Indeed, atraumatic measurement of this interval might yield certain more reliable data than direct methods—particularly its changes in therapeutic and experimental situations—owing to two factors: (1) The patient cannot be "basal" during either chest operation or cardiovascular catheterization. These involve considerable physiological adaptation to the procedure itself, premedication, and use of general or local anesthetic agents, as well as an indeterminate neural and catecholamine response to fear and apprehension, all of which affect the contractile characteristics

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of the myocardium. (2) Left ventricular *movement* appears to precede the onset of cavitary pressure rise (see below). Thus depending on definition of IVCT external detection of the very beginning of left ventricular contraction could be superior to catheter data.

A variety of methods of atraumatically measuring IVCT have been reported. We propose to compare these methods with the results of direct measurement and with each other and to suggest which may be the most reliable.

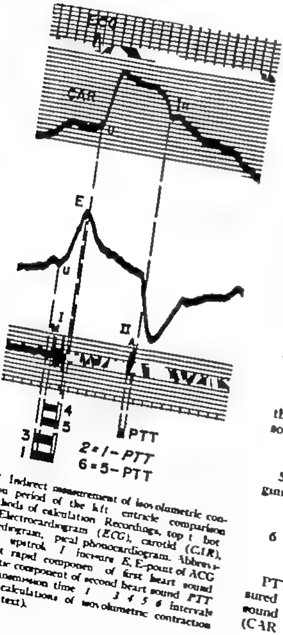

Fig. 1. Indirect measurement of isovolumetric contraction period of the left ventricle: comparison of methods of calculation. Recordings, top to bottom: Electrocardiogram (*ECG*), carotid (*CAR*), apexcardiogram, apical phonocardiogram. Abbreviations: u, upstroke; *I*, incisura; *E*, E-point of ACG; *I*M, first rapid component of first heart sound; *II*, aortic component of second heart sound; *PTT*, pulse transmission time; *1*, 2, *3*, *4*, *5*, *6*, intervals used in calculations of isovolumetric contraction time (see text).

Material and methods

A total of 50 normal active young men in a narrow age range (2? to 35 years) were studied. All had histories of total good health and had no physical, electrocardiographic, or roentgenological signs of heart or other disease. None was significantly obese and none was under any form of medication. Multiple simultaneous cardiographic records were obtained on a Sanborn No. 568-100A eight-channel optical recorder at 75 mm. per second with the subject recumbent and in a relaxed expiratory apnea; these included apexcardiogram (ACG) and phonocardiogram (with the use of the Sanborn No. 62 1500-C13 attachment and crystal microphone No. 374) and right external carotid arteriogram with the Sanborn No. TPS 10 pulse transducer.

Calculations. IVCT was derived from these records by six different measurements (Fig. 1).

1. The interval from the beginning of the ACG upstroke (ACGu) to that of the carotid (CAR) upstroke (CARu).

$$IVCT = ACGu - CARu \qquad (1)$$

2. Method No. 1 corrected for delay in pulse transmission time (PTT) of the central pulse to the carotid artery (see below).

$$IVCT = ACGu - (CARu \text{ minus } PTT) \qquad (2)$$

3. The interval between ACGu and the E-crest of the ACG.

$$IVCT = ACGu - E \qquad (3)$$

4. The interval between the onset of the first rapid vibration of the first heart sound (mitral sound, I_M) and E.

$$IVCT = I_M - E \qquad (4)$$

5. The interval between I_M and beginning of the CARu.

$$IVCT = I_M - CARu \qquad (5)$$

6. Method No. 5 corrected for PTT.

$$IVCT = I_M - (CAR \text{ minus } PTT) \qquad (6)$$

PTT ("carotid delay time") was measured by the interval between the aortic sound (II_A) and the carotid incisura (CAR_{In}).

$$PTT = II_A - CAR_{In}$$

Table I. Isovolumetric contraction period of the left ventricle (comparison of methods of measurement)

	Method					
	1	*2*	*3*	*4*	*5*	*6*
Range (msec.)	70–120	40–90	30–200	20–140	40–100	10–70
Mean	94.1	70.9	97.4	[illegible] 6	61 [illegible]	39.0
S.D.	13.9	13.8	29.6	25.2	14.0	13.9
S.E.	2.1	2.4	4.2	3.6	2.0	2.0

Results

Results of the various calculations are summarized in Table I. The mean values and ranges are rather disparate. Methods 1 and 3 give means of 94.1 and 97.4 msec., respectively. Methods 4 and 5 yield means of 58.6 and 61.8 msec. Method 2 produces 70.9 msec. and method 6 39.0 msec. The narrowest ranges occur in methods 1 and 2, which also produce the least relative scatter (S.D.).

Discussion

The variability of results from different methods of measuring and computing IVCT, each based on formulas reported with confidence by some investigators,[1] [1] leads to an embarrassment of choices, which inevitably raises two questions: (1) How is the IVCT defined and does it require redefinition? (2) What criteria define a satisfactory indirect method of measurement? We shall attempt to answer these in reverse order and in so doing to arrive at a choice of the optimum method of determining IVCT.

Definition of the IVCT. There is agreement that the *end point* of isovolumetric contraction is the onset of ejection. Since indirect recordings cannot be made from the ascending aorta, the time of onset of pressure rise (coincident with outward movement) of the carotid artery is used with subtraction of the time for the pulse wave to travel from aorta to carotid—PTT. This delay appears to be the same at the onset as at the end of ejection[7]; indeed, it is precisely because of this relationship that left ventricular ejection time is so reliably measured from carotid curves.[8] Since the aortic sound (II_A) is virtually coincident with aortic incisura, the PTT is the time between the appearance of II_A and the carotid incisura (CAR_I). For each subject this interval can be deducted from the time of onset of the CARu to indicate the moment of ejection and hence the endpoint of the IVCT.

The exact *beginning* of isovolumetric contraction is not so easily established—both in physiological terms and in points of measurement. Thus, there are three potential isovolumetric contraction periods, each based on a different initial physiological event.

1. THE PERIOD FROM CLOSURE OF THE MITRAL VALVE TO EJECTION. This is the classic IVCT, measured *internally* by the time between crossing of the left ventricular pressure pulse curve first with the left atrial curve and then with the aortic curve. *Externally*, this is approximated by the interval from I_M to the ejection point.

2. THE PERIOD FROM THE BEGINNING OF CAVITARY PRESSURE RISE TO EJECTION. *Internally* this is measured from the onset of the left ventricular pressure curve (which precedes mitral closure) to its crossing of the aortic curve. *Externally*, this can be approximated by the interval from the initial ventricular deflection of the kinetocardiogram (KCG) to the calculated ejection point.

3. THE PERIOD FROM THE EARLIEST DETECTABLE LEFT VENTRICULAR MOVEMENT TO EJECTION. *Internally*, this cannot be measured. *Externally*, this is measured from the

beginning of left ventricular motion to the calculated ejection point. The earliest detectable movement of left ventricular contraction (which precedes the rise of the pressure curve) is first registered by the ACGu; the initial ventricular deflection of the KCG occurs later. This relationship is reflected in the longer electromechanical lag of the KCG (mean = 38 msec.). Our shorter lag for the ACG of 22 msec. agrees with that of Levine's group[1] (21 msec.)

Reasons can be adduced for defining IVCT each way. It appears, however, that for purposes of external measurement, at the very least—and probably also in a physiological sense—it may be preferable to favor definition 3. The evidence for this may be summarized as follows: (1) left ventricular systole actually begins before the rise in left ventricular pressure; indeed, intramural pressure is well set up before cavitary pressure begins to rise,[1,12] (2) this appears to be first detected by the ACG which usually rises before the pressure curve; and (3) the entire period of left ventricular contraction prior to ejection is encompassed. (Fortuitously, the necessarily longer period thus defined reduces the error inherent in measuring smaller intervals.) We shall return to these considerations later.

With the foregoing in mind, it is necessary to define satisfactory indirect measurement before discussing our specific results. To be acceptable, any indirect method must fulfill three postulates.

Postulates for acceptability of indirect methods of measurement

I. Results must duplicate or reasonably approximate those of any comparable direct method.

II. Calculations should be based on measurement reflecting the actual physiological events involved, i.e., if the numerical results are comparable with those of direct methods, this should not be accidental.

III. If more than one calculation fulfills Postulates I and II, the optimum method will be that for which the points measured can be established with greatest confidence in the technique of recording and identification.

In view of these criteria, there are specific objections to certain points used in various formulas for external derivation of IVCT. With regard to the endpoint of IVCT, the E-crest of the ACG is unsatisfactory, primarily because it does not appear to represent the actual onset of ejection[2]; indeed, its timing has a fair though rather variable correlation with the onset of the CARu—which must occur after the beginning of ejection. Indeed, left ventricular ejection times calculated from the E-crest to II do not correlate satisfactorily with more accurate methods of measuring ejection time.[3,4,6] Finally, E often is a fairly broad summit and therefore susceptible to much more error of measurement than the relatively clear points at which the apex and carotid upstrokes depart. With regard to the *beginning* of IVCT, if this interval is defined as commencing with either the initial left ventricular movement (ACGu) or with the beginning of left ventricular pressure rise, it is clear that I_M occurs much too late. Furthermore, even in terms of the classic IVCT beginning with mitral closure, I_M remains a late event; it occurs *after* the crossing of the left ventricular and left atrial pressure curves by as much as 40 msec., i.e., when the mitral valve is already closed and when there is already a relatively large V-A pressure gradient.[13,14]

Our results with each method of external measurement (Table I) may now be examined in the light of the foregoing discussion and in terms of the three postulates delineating satisfactory external measurements.

Calculation 5. IVCT = I_M—CARu = 61.8 ± 14.0 msec. This result is extremely close to that of Braunwald and colleagues[13] (61 ± 12.1 msec.) for an IVCT beginning with the onset of left ventricular pressure rise (Definition 2 above). However, Postulate *II* obviously is not fulfilled since the result is accidental; the remarkable resemblance can be ascribed to a purely fortuitous cancellation of the delay in appearance of I_M by that of CARu.

Calculation 6. IVCT = I_M—(CARu − *PTT*) = *39.0 ± 13.9* msec. This should represent the classic IVCT noted in Definition 1; it agrees well with the 38 msec. mean of Holldack[15] which is based on essentially the same calculation. More

over if the mean of Tafur and associates[1] for the same measurement (PEC II) is reduced by our mean PTT of 26 msec., a similar figure also results (41 msec.). Yet other investigators report rather disparate mean values (Frank and Kinlaw,[4] 49 msec.; Raineri, 30 msec.; and Merlen,[8] 32.5 msec.). The discrepancy of approximately ±10 msec. probably represents variability in recording and measuring I_M—the first rapid vibration of the first heart sound; this means that Postulate III is difficult to fulfill for technical reasons. Even more important, Postulate II cannot be fulfilled since, as already noted, I_M is at best a late phenomenon. Indeed, on these grounds it is difficult to understand the high figure reported only by Frank and Kinlaw.

Calculation 4. IVCT = I_M—E = 58.6 ± 23.[illegible] msec. This yields a result reasonably close to that of Calculation 5, probably because of the general correspondence of the timing of E to that of CARu noted by us[5] and others.[3] It cannot be accepted, both because of the objections already cited for use of I_M and because E does not appear to represent true ejection (Postulate II not fulfilled).

Calculation 3. IVCT = ACGu—E = 97.4 ± 29.6 msec. This result must also be rejected because of the objections cited for using E.

Calculation 1. IVCT = ACGu—CARu = 94.1 ± 13.9 msec. This figure is quite close to that of Tafur and associates for the same measurement (102 msec.), but does *not* allow for PTT. Significantly, its mean of 94.1 msec. is very close to the 97.4 msec. of Calculation 3. This reflects the rough correspondence of E and CARu; the greater scatter in Calculation 3 (S.D. twice that of Calculation 1) reflects the great variability of the E crest.

Calculation 2. IVCT = ACGu—(CARu − PTT) = 70.9 ± 15.8 msec. This result agrees well with that of Oreshkova[2] for the same measurement (67 msec.). Moreover, if our mean PTT of 26 msec. is subtracted from the result of Tafur and associates[1] for Calculation 1 (above), this will yield 76 msec., which also approximates our result. The IVCT of Harrison and co-workers,[7] measured from the "initial ventricular movement" of the kinetocardiogram to CARu − PTT, gave a mean value of about 63 msec. for men in the age group studied by us; since the end points are identical, the difference can be ascribed to the shorter electromechanical lag of the ACG as compared to the KCG.

Calculation 2 appears to be the optimum method for measuring IVCT based on the *inclusive* definition of this period. Indeed, Wiggers[17] considered the period of rising left ventricular pressure in advance of mitral closure "so nearly isometric" as to warrant inclusion in the IVCT. By the same reasoning, the earliest contractile movement of the left ventricle, probably the result of the earliest intramural tension, is no less isometric and therefore cannot be ignored. Indeed, this relationship is clearly indicated in recent studies[11] which demonstrate a relatively steep increment in intramural left ventricular pressure well before cavitary pressure begins to rise.

Conclusions

1. The IVCT is best defined as the total systolic period before ejection, at least for purposes of external measurement and probably also in a physiological sense. Specifically, it commences with the earliest left ventricular movement, which appears to result from rising intramural tension in advance of the cavitary pressure rise.

2. The ACG records left ventricular motion before other external or internal methods; thus IVCT is best measured from the onset of its upstroke (ACGu) to the calculated ejection point. For external measurement, beginning ejection is calculated from the onset of the carotid pulse minus the time taken for pulse transmission from the ascending aorta. Our result for IVCT, therefore, is expressed as follows:

IVCT =
ACGu—(CARu − PTT) = 70.9 ± 15.8 msec.

3. Other methods of calculation appear to give widely divergent values for IVCT based both on the definition of IVCT used (and hence the points measured) and on the variability among investigators for results of the same methods. This variability appears to be due to the use of points of measurement which may

not coincide with actual physiological events or which lack precise definition in recording (An exception to this is the use by Harrison and co-workers[7] of the initial ventricular movement of the KCG which appears to approximate the beginning of left ventricular cavitary pressure. IVCT measured from this point to the calculated ejection point reflects a period which is susceptible to internal measurement but it is shorter than that using the ACG owing to the greater electromechanical lag of the KCG and does not include the period of rising mural pressure.)

Summary

The isovolumetric contraction period of the left ventricle (IVCT) was measured atraumatically by six different cardiographic methods in 50 normal young men IVCT has been redefined as the total period of left ventricular contraction prior to ejection—i.e. the period of left ventricular mural tension + the period of rising cavitary pressure. The ACG detects the earliest inception of left ventricular systole both for accuracy of indirect measurement and physiologically the onset of its upstroke appears to be the beginning of isometric contraction. Our results for this period are 70.9 ± 15.8 msec., with the ejection point calculated by deduction of the PTT from the carotid upstroke. The results of other methods of calculation and other points of measurement are compared and discussed

REFERENCES

1 Tafur E., Cohen, L. S., and Levine, H D The normal apexcardiogram. Its temporal relationship t electrical, acoustic and mechanical cardiac events, Circulation 30:381 1964.
2. Oreshkove, V Indirect measurement of isovolumetric contraction time on the basis of polygraphic tracing, Cardiologia 47:315 1965
2a. Holldack, K. Cited by Oreshkove.
3. Benchimol, A., and Dimond, E. G. The normal and abnormal precardiogram. Its physiologic variation and its relation t intracardiac events, Am. J Cardiol. 12:368, 1963.
4. Raineri, A. Il cardiogramma apicale nella valutazione della dinamica cardiaca, Boll. Soc. Ital. Cardiol. 10:64, 1965.
5. Merlen, J F La phase isométrique de la systole ventriculaire, Actual. cardioangeiol. Int. 14:119 1965.
6 Frank, M N and Kinlaw W B. Indirect measurement of isovolumetric contraction time and tension period in normal subjects Am. J Cardiol. 10:800, 1962.
7 Harrison T R., Dixon, K., Russell, R. O J Bidwai, P S., and Coleman, H. N The relationship of age to the duration of contraction ejection, and relaxation of the normal human heart, Am. Heart J 67 189 1964.
8. Weissler A. M Peeler R. G., and Roehll, W H., J Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease, Am Heart J 62:367 1961
9 Spodick, D H., and Kumar S. Left ventricular ejection period, Am. Heart J (In press)
10. Spodick, D H and Kumar S Electromechanical lag of the left ventricle. I preparation.
11. Dieudonne, J M Tissue-cavitary difference pressure of dog left ventricle Am. J Physiol. 213 101 1967
12. Rios, J C., and Massumi, R. A. Correlation between the apex cardiogram and left ventricular pressure, Am. J Cardiol 15:647 1965.
13. DiBartolo, G., Nunez-Dey D M iesan, G., MacCanon, D M., and Luisada, A A. Hemodynamic correlates of the first heart sound, Am. J Physiol. 201:888, 1961
14. Luisada, A. A., and Allmarung, N M An encyclopedia of the cardiovascular system, in Luisada, A. A., editor Cardiology Vol. 1 New York, 1959 McGraw Hill Book Co., Inc., pp. 2-92.
15. Braunwald, E., Fishman, A P and Cournand, A. Time relationships of dynamic events in the cardiac chambers, pulmonary artery and aorta in man, Circulation Res. 4 100, 1956.
16. Holldack, K. Atlas nd kurzgefasstes Lehrbuch der Phonokardiographie, St ttgart, 1956, Thieme Verlag, p. 39
17 Wiggers, C. J Studies on the consecutive phases of the cardiac cycle. I. The duration of the consecutive phases of the cardiac cycle and the criteria for their precise determination, Am. J Physiol 56:415, 1921

Fibrinolytic and thromboplastic activity of normal human heart valves

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The fibrinolytic and thromboplastic activities of the large human vessels show interesting patterns of distribution. The adventitial layers are always highly fibrinolytic. While extracts of the arterial intima show considerable thromboplastin content with little or no fibrinolytic activity, the venous intima, in contrast, is markedly fibrinolytic.[1,2] The distribution in animal vessels differs from that in man. Fibrinolytic activity is related to endothelial cells of veins and venules but is usually absent from the arterial endothelium.[3,4] It is believed that differences in tissue repair observed in response to injury of the vessel wall could in part be caused by such variations. To elucidate the conditions prevailing at the interior surfaces of the heart, the fibrinolytic and thromboplastic activities of the valves of the normal human heart were determined.

Material and methods

A total of 15 normal human hearts were obtained fresh from autopsy from subjects ranging from 32 to 82 years in age. The hearts appeared grossly normal and there was no history of endocarditis. Slight or moderate nodular thickenings were observed in the atrioventricular valves along the lines of closure over the insertions of the chordae tendineae. Some authors consider these formations, which were present in all age groups, to be a response to tensions caused by normal valve movements. All valves were dissected into a proximal and distal part. The chordae tendineae were also isolated. Each specimen was carefully rinsed, dried between absorbent paper, weighed, and stored in tightly closed vials at $-20°$ C for no longer than a week.

Assay of plasminogen activator

POTASSIUM THIOCYANATE (KSCN) (REAGENT GRADE) 2 M. Daily adjusted to pH 7.75 with solid $NaHCO_3$.

KSCN 1 M WITH 0.25 PER CENT GELATINE. Gelatine (500 mg, bacteriological) was dissolved in 100 ml. of warm water and added to 100 ml. of 2 M KSCN. Adjusted to pH 7.75 as above.

FIBRIN PLATE BUFFER. Barbital buffer (0.05 M) containing 0.09 M NaCl, 1.7 mM $CaCl_2$, and 0.7 mM $MgCl_2$, pH 7.75, total ionic strength 0.15.

Solutions of bovine plasminogen-rich

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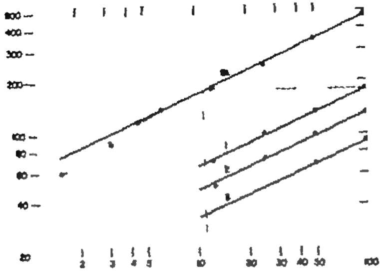

Fig. 1. Plasminogen activator assay in mitral valve. Abscissa: concentrations in per cent of stock solution (logarithmic). Ordinate: activity in diameter products of 2 perpendicular diameters in square millimeters of lysed zones (average of triplicate; logarithmic). The pig heart standard solution contained 19 tissue activator units per milliliter.

Calculations: curve 1, chordae tendineae. Stock solution produced by 179 mg. of tissue in 5.4 ml. 2 M KSCN. The stock solution (100 per cent) has the same activity as 11 per cent of the standard stock solution. Hence, the concentration of plasminogen activator in the sample is $\frac{19 \times 11}{100}$ units per milliliter. The total 5.4 ml. obtained from 179 mg. yields $\frac{19 \times 11 \times 5.4 \times 1{,}000}{100 \times 179} = 63$ units per gram of fresh tissue; curve 2, mitral valve, proximal part, 280 mg. in 8.4 ml. Activity 5.3 per cent of standard yielding 37 units per gram; curve 3, mitral valve, distal part, 300 mg. in 9.0 ml. Activity 3 per cent of standard yielding 17 units per gram.

fibrinogen prepared by ammonium sulfate precipitation,[7] containing 1 to 2 per cent fibrinogen and with an ionic strength (μ) of 0.45 were diluted with 2 volumes of water and then further diluted with fibrin plate buffer to a fibrinogen concentration of 0.1 per cent.

Plasminogen activator was assayed as before[4,8] with improvements to be reported in detail elsewhere. The procedure briefly described was as follows: specimens were cut into small pieces and treated in a Potter-Elvehjem homogenizer (cooled in ice water) with 3 ml. of 2 M KSCN per 100 mg. of tissue followed by slow mechanical shaking for one hour at room temperature and separation of the supernatant by centrifugation. Next, when the usual acid precipitation procedure was followed, the heart valve extracts gave incomplete precipitation leaving a turbid active supernatant, even after prolonged centrifugation at high speed. However, addition of an extract from rabbit skeletal muscle which contains neither plasminogen activator nor inhibitory compounds produced complete separation. Therefore, to an aliquot (1 ml.) of the supernatant were added 6 ml. of water and 1 ml. of an extract of rabbit skeletal muscle in 2 M KSCN. After acidification to pH 1.00 and centrifugation, the sediment was dissolved in 1 ml. of 1 M KSCN containing gelatine, adding solid $NaHCO_3$ until neutral on litmus paper. Each solution thus prepared was serially diluted with 1 M KSCN (with gelatine) and assayed in triplicate on fibrin plates using disposable Petri dishes selected for flatness (Falcon Plastics, 8.4 cm. inside diameter). Fibrinogen solution (9 ml.) was clotted with 0.3 ml. of thrombin solution (bovine,* 20 units per milliliter in saline). After incubation for 15 to 18 hours at 37° C., the diameter products (in square millimeters as average of each triplicate) were plotted against relative

*Leo Pharmaceuticals, Copenhagen, Denmark.

concentrations in a double logarithmic graph (Fig 1) Concentrations of tissue plasminogen activator per milliliter were determined by interpolation on a reference curve simultaneously assayed and converted into units per gram of fresh tissue Tests for unspecific protease activity were performed on fibrin plates heated at 85° C for 45 minutes to destroy plasminogen

Histochemical fibrin slide technique To localize the plasminogen activator valves of 5 hearts were studied by the histochemical method[4,5,19] Frozen sections, cut at 6 to 8 μ were placed on slides and covered with a layer of fibrin (produced by plasminogen rich fibrinogen[7] 0 7 per cent in phosphate buffer of pH 7 75) approximately 60 to 80 μ thick. After incubation of the slides in a moist chamber at 37° C for an appropriate length of time followed by fixation in formalin and staining with Harris hematoxylin the localization of lysed zones of fibrin can be topographically correlated with tissue structures of the section

Assay of tissue thromboplastin Human blood collected in plastic tubes in one-tenth volume of 3 2 per cent of sodium citrate was spun at 15 000 r.p.m (2 700 g in a refrigerated centrifuge and the platelet poor plasma transferred to siliconized glass vials and stored at −20° C.

Saline-barbital buffer with gelatine pH 7 75 0 05 M of sodium barbital in 0 1 M NaCl (total ionic strength 0 15) containing 0 25 per cent gelatine

$CaCl_2$ 0 03 M Two volumes of saline-barbital buffer were added to 3 volumes of 0 05 M $CaCl_2$

Tissue samples were treated in a Potter Elvehjem homogenizer with 0 9 ml of saline barbital buffer (with gelatine) per 100 mg of tissue cooling the outside in ice water The suspension was frozen overnight at −20° C thawed and rehomogenized Serial dilutions were prepared in saline-barbital buffer (with gelatine) Each dilution was assayed in a system consisting of 0 2 ml of citrated platelet poor plasma (freshly thawed and kept in ice water during experiments) 0 1 ml of saline-barbital buffer (with gelatine) and 0 1 ml of the tissue thromboplastin dilution. The mixture was pre-

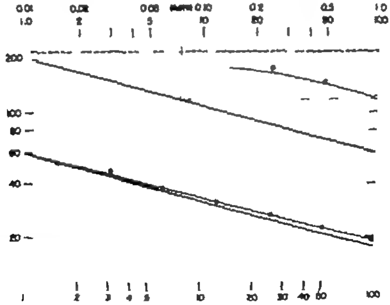

Fig. 2 Assay of tissue thromboplastin in mitral valve. Abscissa: thromboplastin units (logarithmic). *Ordinate:* clotting times in seconds (logarithmic). The lower full curve refers to values ranging from 1.0 to 100 units and the upper *full curve* to values ranging from 0 01 to 1.0 unit. Curve 1 (full circles) is a control curve with Simplastin. Curve 2 (open circles) is an assay of the distal portion of the mitral valve.

It can be seen that at the 100 per cent concentration of Curve 2 the clotting time 120 seconds corresponds to 0.076 units. Since this is present in 0.1 ml, which represent 10 mg of tissue there are 7.6 units per gram of fresh tissue.

pared in unsiliconized glass tubes and preheated for 3 minutes at 37° C. before recalcification with 0.2 ml. of the preheated 0 03 M $CaCl_2$-solution Clotting times were determined in a coagulometer[11] in seconds (average of duplicate) and plotted against relative concentrations in a double logarithmic graph (Fig 2) Concentrations of tissue thromboplastin were determined as before[12] and calculated in units per gram fresh tissue. In the present study one thromboplastin unit was arbitrarily defined as the amount of tissue thromboplastin producing coagulation of the human plasma mixture in 60 seconds. Since human plasma is less sensitive to tissue thromboplastin than the rabbit plasma previously used the present unit differs from the former unit.[12] It is approximately twice as large. The reproducibility and in particular the constancy of the slope of the straight line obtained in the double logarithmic plot was controlled with Simplastin (a calcium-free preparation) The content of a Simplastin vial was treated in the homogenizer with 4 ml of H_2O and 6 ml of saline-barbital buffer (with gelatine) distributed in small vials and stored at −20° C. Each small vial was used only once. Conversion of clotting times to concentrations was justified by a reasonable constancy of the slope and position of the Simplastin curve throughout our investigations. With 15 batches of human plasma, the slope ranged from 0.23 to 0.?75 with an average of 0 26 The position as determined by the clotting times read from the dilution curves at 100 per cent concentration ranged from 16 5 to 22 5 seconds averaging 19 9 seconds.

*Warner-Lambert Research Institute, Morris Plains, N. J courtesy of Dr George Phillips

Results

A determination of plasminogen activator in a mitral valve with its chordae tendineae is shown in Fig 1 All assays were performed in the manner described The results show large individual variations (Table I) agreeing with previous determinations of individual values of tissue plasminogen activator concentration[12] In the proximal parts of the atrioventricular valves the average concentrations were slightly higher than in the distal parts. In the semilunar valves all values were low The average concentrations in the chordae tendineae were intermediate between the former None of the extracts produced lysis on heated fibrin plates

Table I Plasminogen activator concentrations in units per gram of fresh tissue

Age	Sex	Patient A	Mitral valve			Tricuspid valve			Aortic valve		Pulmonic valve	
			Proximal	Distal	Chordae tendineae	Proximal	Distal	Chordae tendineae	Proximal	Distal	Proximal	Distal
54	F	1	92	21	—	35	35	—	—	30	33	—
[illegible]	F	2	18	7	14	[illegible]	5	26	4	11	5	0
59	F	3	42	13	21	49	18	31	13	6	19	22
57	F	4	8	11	11	0	0	8	14	18	0	[illegible]
—	—	5	37	14	16	33	13	15	21	18	4	11
47	F	6	18	13	53	20	19	60	16	14	7	14
66	M	7	97	24	68	22	11	14	[illegible]	60	16	11
47	F	8	32	17	63	120	21	23	13	21	19	29
34	M	9	25	14	9	23	8	8	11	18	17	13
32	M	10	22	8	6	83	0	5	8	7	10	7
45	—	11	14	10	—	38	31	—	11	11	—	6
82	F	12	50	16	13	31	[illegible]	44	35	20	14	[illegible]
Average			38	13 5	28	41	15	23	15	19 5	[illegible]	12

Table II Concentration of tissue thromboplastin in arbitrary units per gram of fresh tissue

Age	Sex	Patient N	Mitral valve			Tricuspid valve			Aortic valve		Pulmonic valve	
			Proximal	Distal	Chordae tendineae	Proximal	Distal	Chordae tendineae	Proximal	Distal	Proximal	Distal
54	F	1	< 1	< 1	—	1	1	—	3	3	< 1	< 1
68	F	2	35	3	3	8	11	1	3	3	1	2
57	F	4	3	3	—	15	8	15	3	3	3	6
47	F	6	100	24	—	6	6	—	—	—	57	8
47	F	8	32	8	2	11	4	—	8	5	2	2
34	M	9	3	3	3	2	2	—	3	2	2	3
32	M	10	1	2	—	2	2	—	—	—	—	—
45	—	11	1	1	—	3	1	—	1	1	1	1
82	F	12	1	3	3	27	1	8	1	—	1	—
64	—	13	4	4	—	8	8	—	6	8	6	6
Average			18	5	3	8	4	8	4	3	8	4

indicating that nonspecific protease activity was absent

Fig 2 is an assay of tissue thromboplastin in the distal part of a mitral valve The reference curves are drawn on the basis of the average values obtained from 15 different batches of substrate plasma The control curve was included to ascertain that the substrate plasma used produced curves parallel (within the experimental accuracy) with the reference curves. Concentrations are calculated and converted into units per gram tissue as described The broken line represents the recalcification time of the substrate plasma under the experimental conditions. Table II shows that the average thromboplastin concentration is extremely low in all types of valves The slightly higher average concentration in the proximal part of the mitral valve is caused by a few individual values.

Neither the fibrinolytic assays nor the thromboplastin determinations showed any relation to age or sex. When the data were arranged according to increasing fibrinolytic activities, a patient was sometimes seen to exhibit the same pattern of activity through all of the assays but this tendency was not uniform

In 2 of the 5 hearts studied histochemically fibrinolytic activity was found related to vessels present in the inner third of the atrioventricular valves (Fig 3) as well as to sites at the endocardial lining (Fig 4) Sections of an aortic semilunar valve (Fig 5) and of a tricuspid valve (Fig 6) suggest that fibrinolytically active sites are present at the endocardium where cell dislocation has occurred Imprints made by applying the surface of an aortic valve to a frozen glass slide showed after 30 minutes of incubation fibrinolytic activity related to single endocardial cells (Fig 7)

The fibrinolytic activity in the chordae tendineae could be related to the presence of vessels. Fig 8 shows a section of a chorda adjacent to its attachment to the papillary muscle In such sections, vessels could be demonstrated in nearly all chordae These vessels run mostly under the endocardial lining and fibrinolytic activity is related to them There were no vessels in the remaining parts of the chorda and only occasionally did weak fibrinolytic activity occur at sites on the endocardial lining

Discussion

Compared with the concentration of plasminogen activator in most human organs[11,3] the concentrations in the heart valves are very low The low content of thromboplastin is also striking The combi-

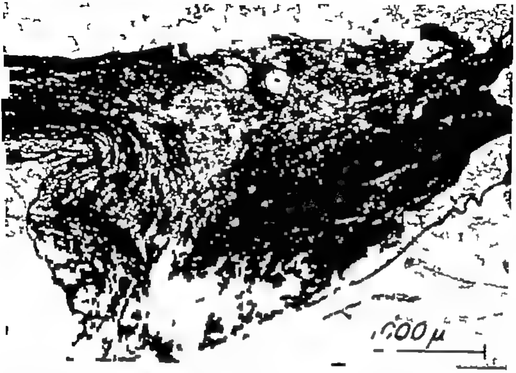

Fig. 3. Cross section of inner third of mitral valve. Lytic zones related to 2 blood vessels. Incubated 40 minutes.

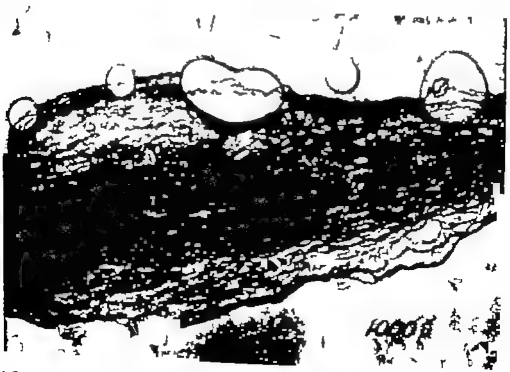

Fig. 4. Cross section of inner third of another mitral valve. Lysis in relation to blood vessels and to endocardial lining. Incubated 40 minutes.

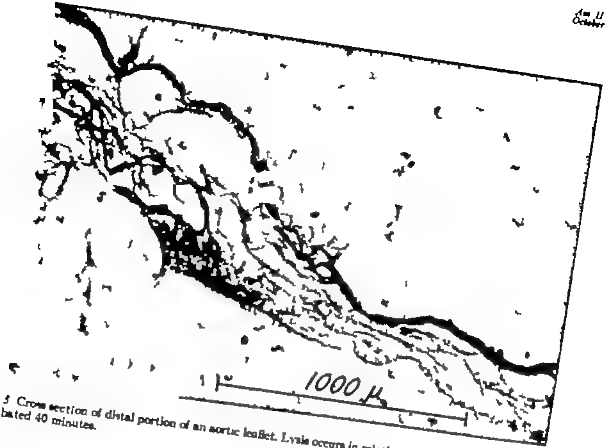

Fig. 5. Cross section of distal portion of an aortic leaflet. Lysis occurs in relation to dislocated endocardial cells. Incubated 40 minutes.

Fig. 6. Cross section of proximal portion of a tricuspid valve (from same heart as in Fig. 4). Lysis in relation to sites at endocardial lining. Incubated 40 minutes.

Fig. 7. Lysis produced by single endocardial cells (from same aortic leaflet as in Fig. 5). Incubated 40 minutes.

Fig. 8. Chorda tendinea of mitral valve. Cross section of portion adjacent to attachment to papillary muscle. Lysis in relation to subendocardial muscle and to endocardial lining. Incubated 40 minutes.

nation of low fibrinolytic and low thromboplastic activity makes the heart valves similar to the synovial joint tissues.[11] Noteworthy is the absence of marked differences between the left and the right side of the heart. This finding was unexpected because the endocardium is continuous with the endothelium of the vessels where large differences were observed.

It is perhaps not surprising that the heart valves contain little plasminogen activator. Their tendinous membrane is a connective tissue structure in which fibrinolytic activity has never been localized. Its content of hyaluronic acid[7] could possibly explain the assay difficulties. On the fibrin slides lysed areas appeared after incubation periods of 30 to 45 minutes, indicating a low activity. Highly active vascular structures, such as budding capillaries, often produce lysis after only 5 minutes of incubation. Normal human heart valves are avascular except for the most proximal parts of the mitral and tricuspid valves,[12,13] which could explain the increase in plasminogen activator in the proximal parts of both atrioventricular valves (Table I). The localization of fibrinolytic activity in parts of the chordae tendineae close to the papillary muscle is of interest in view of controversies existing about the vascularization of these structures.

The presence of weak fibrinolytic activity at sites related to an ordinarily inactive endothelial surface requires special comments. The active sites appear to be located at areas of beginning cellular dislocation (Figs. 5 and 6). Though the preparation of sections of these delicate structures is difficult, it is believed that this observation is true and not due to an artifact. Rarely was activity observed on an undisturbed endothelial lining except when related to vessels, though the identification of vessels in these structures presented difficulties (Fig. 4).

There have been many speculations about the etiology and pathogenesis of valvular disease. The finding of a low content of tissue thromboplastin would suggest that there is little tendency for tissue thromboplastin induced fibrin formation after injury at valvular surfaces. However, platelet agglutination on an injured surface followed by activation of the intrinsic blood coagulation system might eventually build up more fibrin than could be removed by the low fibrinolytic activity present in the tissues, ultimately leading to fibrosis. Our observations tend to substantiate the concept that the chief etiological factor of valvular disease is of a hemodynamic rather than of a hemostatic nature.

Summary

Human atrioventricular valves, with their chordae tendineae, and semilunar valves were assayed for their content of tissue thromboplastin and plasminogen activator. Concentrations of tissue thromboplastin as well as of plasminogen activator were low in all samples. Localization of fibrinolytic sites was studied by the histochemical fibrin slide technique. Fibrinolytic activity could be related to vascular structures present primarily in the proximal parts of the atrioventricular valves and the parts of the chordae tendineae close to the attachments to the papillary muscles. In the distal parts of the atrioventricular valves and the semilunar valves there were few sites of fibrinolytic activity, all related to the endocardial lining. The relation of these observations to the vascularization of the valves and the chordae tendineae is discussed. The absence of any significant differences between the left and right side of the heart precludes that the prevalence of valvular disease on the left side is caused solely by a local hemostatic difference.

The skilled technical assistance of Miss Kathryn Pennypacker is acknowledged.

REFERENCES

1. Astrup, T., Albrechtsen, O. K., Claassen, M., and Rasmussen, J.: Thromboplastic and fibrinolytic activity of the human aorta, Circulation Res. 7:969, 1959.
2. Coccheri, S., and Astrup, T.: Thromboplastic and fibrinolytic activity of large human vessels, Proc. Soc. Exper. Biol. & Med. 108:369, 1961.
3. Astrup, T., and Buluk, K.: Thromboplastic and fibrinolytic activities in vessels of animals, Circulation Res. 13:253, 1963.
4. Todd, A. S.: The histological localization of fibrinolysin activator, J. Path. & Bact. 78:281, 1959.
5. Kwaan, H. C., and Astrup, T.: Localization of fibrinolytic activity in the eye, Arch. Path. 76:595, 1963.

6. Warren, B. A.: Fibrinolytic properties of vascular endothelium, Brit. J. Exper. Path. 44:365, 1963.
7. Brakman, P.: Fibrinolysis, Amsterdam, 1967, Scheltema and Holkema.
8. Astrup, T., and Mullertz, S.: The fibrin plate method for estimating fibrinolytic activity, Arch. Biochem. 40:346, 1952.
9. Astrup, T., and Albrechtsen, O. K.: Estimation of the plasminogen activator and trypsin inhibitor in animal and human tissues, Scand. J. Clin. & Lab. Invest. 9:233, 1957.
10. Kwaan, H. C., and Astrup, T.: Demonstration of cellular fibrinolytic activity by the histochemical fibrin slide technique, Lab. Invest. 17:140, 1967.
11. Schnitger, H., and Gross, R.: Über ein Universalgerät zur automatischen Registrierung von Gerinnungszeiten, Klin. Wchnschr. 32:1011, 1954.
12. Astrup, T.: Assay and content of tissue thromboplastin in different organs, Thromb. Diath. Haemorrh. 14:401, 1965.
13. Astrup, T.: Tissue activators of plasminogen, Fed. Proc. 25:42, 1966.
14. Albrechtsen, O. K.: The fibrinolytic activity of human tissues, Brit. J. Haemat. 3:284, 1957.
15. Astrup, T., and Sjölin, K. E.: Thromboplastic and fibrinolytic activity of human synovial membrane and fibrous capsular tissue, Proc. Soc. Exper. Biol. & Med. 97:852, 1958.
16. Kirk, J. E.: Thromboplastin activities of human arterial and venous tissue, Proc. Soc. Exper. Biol. & Med. 109:890, 1962.
17. Torii, S., and Bashey, R.: High content of hyaluronic acid in normal human heart valves, Nature 209:506, 1966.
18. Wearn, J. T., Bromer, A. W., and Zschiesche, L. J.: The incidence of blood vessels in human heart valves, Am. Heart J. 11:22, 1936.
19. Harper, W. F.: The structure of the heart valves, with special reference to their blood supply and the genesis of endocarditis, J. Path. & Bact. 57:229, 1945.
20. Clarke, J. A.: An x-ray microscopic study of the blood supply to the valves of the human heart, Brit. Heart J. 27:420, 1965.

Skin-electrode impedance problems in electrocardiography

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One of the significant sources of error in electrocardiographic (ECG) and vectorcardiographic (VCG) recording is at the electrode to skin interface. High and often unpredictable impedances existing at these interfaces can cause considerable distortion in the recording. A number of investigators have reported on the problem of the variability of skin to electrode impedance[1] and have suggested the use of buffer amplifiers in each electrode to minimize errors from this source.[1-4] The most recent report on recommendations for ECG and VCG recording by a committee and subcommittee of the American Heart Association[5] has recognized this problem by including a requirement for a minimum input impedance of 500 000 ohms between any active patient electrode and ground.

The present report concerns a study of the ECG effects of skin to electrode impedance. Although the essential results were obtained using the Frank corrected orthogonal lead system, it is shown that the conclusions apply equally well to the standard leads. Changes in the cardiac potentials as a function of time are also demonstrated to be caused by the time dependent electrode to skin impedance variations.

Material and methods

The Frank lead system[6] was used for recording ECG's on 24 patients onto FM tape. One set of recordings was taken using standard Frank leads through the Frank resistor network having a value of 50 000 ohms for the unit resistor. The 3 preamplifiers used had differential input impedances on the order of 8 megohms. A second set of recordings was taken using the same Frank resistor network, but with a buffer amplifier for each electrode. The electrodes, which were not removed between recordings, were applied to each patient using a commercially available electrode paste and the technique of application was left to the technician to perform in his usual manner consisting of little or no skin preparation beforehand. The electrodes* remained in place 15 minutes for each patient and recordings were taken as soon as the electrodes were

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*All electrodes were square shaped silver alloy plates approximately 2.5 cm. on each side.

in place and at 5-minute intervals thereafter. All patients except one were men varying in age from 25 to 60 years.

The buffer amplifiers, having approximately 3 megohms input impedance and a voltage gain of 0.985 ± 0.005 were similar to those suggested by Schmitt. Each buffer was packaged integrally with the electrode to form a potted unit (Fig 1). Two signal leads were brought out of each buffer package to permit the recording of the lead either with or bypassing the buffer. Fig 2 demonstrates the wiring arrangement. Although the input capacitance of the buffer amplifiers was low enough to have negligible effect at ECG frequencies, it was recognized that the approximately

Fig 1 Photograph of encapsulated buffer amplifier integral with electrode

150 pf capacitance of the bypass signal-lead cable would contribute to errors in which magnitude would depend on the skin to electrode impedance and frequency. The order of magnitude of such errors can be surmised by considering a somewhat extreme case of a 100 K skin to electrode impedance at 100 Hz. The error in measured potential caused by the 100 pf capacitance would be less than 0.5 per cent in amplitude with a phase shift of less than 1 degree. These errors were not considered in this report.

The system bandwidth for recording onto FM tape was 0.05 to 1,250 Hz. In order to utilize a digital computer for performing measurements, the records were digitized at a sampling rate of 1.0 msec. per lead to a precision of approximately 0.1 per cent, using techniques described previously. Measurements were made on 3 consecutive complexes for each of the records to insure that any deviations from one record to another were significantly greater than any beat-to-beat variations. A recording of respiration was taken simultaneously with the 3 leads. This permitted the sampling of the data to be made during similar phases of the respiratory cycle.

At the 5-minute intervals, immediately following each set of recordings, the skin to electrode impedance was measured at

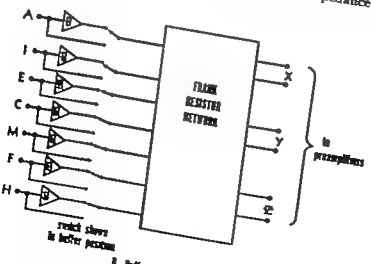

Fig. Wiring arrangement to permit recording of Frank leads either using buffer amplifiers or bypassing them.

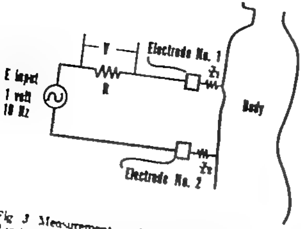

Fig. 3. Measurement method for determination of skin to electrode impedance. Z_1 and Z_2 represent the impedances to be measured. If assumed to be resistive, they may be represented as R_1 and R_2 (see Appendix).

each electrode site. These measurements were made using an input current varying between 10 and 60 microamperes at 10 Hz (Fig. 3 and Appendix). This measurement method permitted a precision of better than 10 per cent for the calculation of skin to electrode impedance values. The total time required to record 2 sets of three lead ECG's (1 with and 1 without buffers) plus the time required to measure all skin to electrode impedances was less than 1½ minutes.

The ECG parameters that were measured by the digital computer* for use in comparing data were Q, R, S, and T wave peak amplitudes for each of the X, Y, and Z leads.

Results

Of the 24 patients studied, the skin to electrode impedance values varied from zero (less than 500 ohms) to over 200,000 ohms. As has been observed by Spach and co-workers, the values obtained were unpredictable from subject to subject and from one electrode to another on any one subject. For example, on one patient whose electrode impedance was 206 K at the E (sternum) position, the impedance was zero at the H (head) position.† However, there was at least one electrode position for which the impedance exceeded 10 K for every one of the 24 patients. One notable observation was that the H position for every patient but one had an impedance less than 6 K. Impedances of 10 K or less were measured on 19 of the 24 patients for electrode position M (back) and on 15 patients for electrode position C (midway between sternum and left midaxillary line), but the impedances at all other electrode positions (with the exception of H noted above) were more often greater than 10 K. The impedance values usually decreased over the 15-minute period; however, in about 10 per cent of the measurements, impedance values increased slightly with time. Often the final impedance value was on the order of 50 per cent of the initial value. Table I lists the values of impedance for all the patients.

Table II lists the errors obtained in 17 of the 24 patients when amplitudes with and without buffers were compared. These differences were greatest for the initial recordings and usually decreased steadily over the 15-minute period. The amplitude values measured using the buffer electrodes remained essentially unchanged, while those using the electrodes without buffers did change over the 15 minute period. Since these changes correlated closely with skin to electrode impedance variations, this demonstrated that the correct ECG values were those obtained using the buffers. In these 17 patients, the X lead was affected in all cases, the Z lead in 10 cases, and the Y lead in 4 cases. Errors in the Q, R, S, and T amplitudes usually exceeded 20 per cent and often exceeded 50 per cent for the initial recordings; the errors usually tended to decrease with time.

Discussion

Skin impedance and skin resistance. To avoid the confusion that sometimes exists between the terms impedance and resistance, the standard definitions as used in electrical engineering terminology will be used. By resistance R we imply the existence of a component which obeys Ohm's law for all frequencies, that is, the voltage E across it and the current I

*Control Data Corporation 3300.
†At this laboratory, the forehead is used for the H electrode position in order to minimize muscle potential interference.

Table I

Patient	Electrode position						
	E	*H*	*F*	*C*	*M*	*I*	*RL*
1	4-5	0-0	6-7	6-7	6-7	3-3	17 16
2	0-0	0-0	60-33	5-3	15-10	66-33	30-16
3	107-47	3-2	40-24	23-18	23-14	40-30	50-43
4	13-11	4-3	97 101	61-45	21 11	41 21	61 56
5	69-47	9-16	2 3	37 21	4-4	36-19	21 14
6	30-16	6-3	16-16	6-3	10-3	39-36	51 37
7	22-17	1 1	43-43	12 12	3-3	1 1	18-18
8	13 9	0-3	11-9	3-3	3-3	4-2	17-9
9	1-4	0-4	42 34	34-37	1-4	51-45	59-36
10	62 32	0-0	8-8	97 79	10-9	22-12	11 11
11	9-7	0-2	7 10	10-8	4-5	7 5	16-10
12	20-14	3-2	36-30	1 2	8-6	18-13	37 27
13	206-139	0-0	67-64	9-4	9-7	47-42	34-31
14	2 2	4-0	8-5	4-2	2 2	3-1	17-8
15	8-13	0-0	9-8	16-12	5-7	14-11	11-8
16	10-9	3-0	23 16	4-1	1-0	5-4	15-12
17	21 21	1 1	2 2	9-9	4-4	3-3	5-5
18	46-35	0-0	42 35	9-6	22 12	0-0	31 26
19	3-2	2-0	31 33	5-3	6-6	9-8	7 7
20	6-3	0-0	12 5	6-4	8-7	1-0	9-8
21	3-2	2-0	3-2	6-5	6-5	5-2	24-21
22	87 17	0-0	29-62	8-7	16-9	23-17	24-23
23	120-37	1-4	30-25	33-17	3-4	24-9	37 36
24	74-36	0-0	9-12	37 27	10-6	5-4	16-11

*Magnitudes of skin to electrode impedance at [illegible] Hz for 24 patients, in kilohms. The values for each entry are the initial and 15-minute values. (The values for electrode position A have been omitted because of faulty connection which was discovered after the measurements were made.)

through it are linearly related for all frequencies, as E = IR. By impedance Z, we imply the existence of a component through which the current is dependent on both the applied voltage and its frequency a capacitor is such a component. In the skin to electrode case, we are concerned with impedance since a capacitive as well as a resistance component is involved In the case of an impedance a phase shift exists between applied voltage and current through the impedance, and this phase shift is dependent on frequency The pure resistance exhibits no such phase shift at any frequency A component which is known to be an impedance is often referred to as a resistance because its impedance (phase shift) effects may be insignificant in the range of frequencies of interest Thus for example the input impedance of an ECG preamplifier is usually referred to as an input resistance because its capacitive effects in the range of ECG frequencies is negligible Similarly although the skin to electrode properties are those of an impedance it is possible to treat it as mainly resistive in nature in certain frequency ranges.

Skin impedance measurements carried out using a variety of different electrode areas and electrode pastes demonstrate that the impedance varies with frequency i.e. there is a substantial capacitive component involved Spach and co-workers[4] showed this effect accounting for impedance values that varied from about 40 k at 5 Hz to about 00 ohms at 1 000 Hz Geddes and Baker[4] demonstrated this effect for subcutaneous needle electrodes. Although an equivalent circuit may be produced to represent this impedance (Fig 4) these authors point out that the R and C values

Table II*

Patient No.	Lead	Time (min.)	Q Amplitude (mv.)	Q % Diff	R Amplitude (mv.)	R % Diff	S Amplitude (mv.)	S % Diff	T Amplitude (mv.)	T % Diff
2	X	0	0.09	—	1.12	−37	0.123	—	0.418	−64
		15	0.09	—	1.16	−21	0.123	—	0.383	−26
3	X	0	0.157	−71	1.39	−11			0.530	−50
		15	0.154	−33	1.37	−7			0.490	−28
4	X	0			0.942	−24	0.185	−33	0.462	−43
		15			0.955	−13	0.173	−26	0.367	−17
5	X	0			1.95	−27	0.28	+93	0.77	−40
		15			1.95	−18	0.25	+32	0.77	−22
	Z	0	0.909	−6	0.940	−31			0.164	—
		10	0.848	−6	0.902	−17			0.087	—
6	X	0					0.097	−75	0.139	−64
		10					0.087	−61	0.078	−24
9	X	0			1.63	−26	0.096	+10	0.151	−66
		15			1.63	−18	0.049	+200	0.237	−66
	Y	0			0.805	−19				
		15			0.770	−30				
	Z	0			1.51	−22				
		15			1.48	—				
10	X	0			1.17	−42	0.117	+100		
		15			1.15	−29	0.093	+83		
	Z	0			0.74	−24				
		15			0.75	−4				
12	X	0			1.7	−16				
		15			1.58	−13				
	Z	0			1.21	−20				
		15			1.10	−10				
13	X	0			0.91	−50	0.270	+78	0.240	−59
		15			0.871	−32	0.262	+62	0.224	−54
	Y	0	0.263	−35	1.50	−6	0.219	—	0.288	—
		15	0.249	−36	1.46	−5	0.224	—	0.265	—
	Z	0	0.365	−45	0.750	−58	0.160	−62		
		15	0.345	−34	0.758	−48	0.144	−50		
15	X	0			0.951	−16				
		15			0.990	—				
18	X	0			1.77	−15	0.35	+20	0.57	−29
		15			1.80	−3	0.32	+18	0.49	—
	Y	0			0.74	−9			0.21	—
		15			0.72	—			0.18	—
	Z	0			0.95	−13				
		15			0.98	−17				
19	X	0			1.76	−13				
		15			1.75	−10				
	Y	0			0.78	−10				
		15			0.76	−8				
20	X	0			0.87	−11				
		15			0.83	—				
	Z	0	0.31	−20	0.67	−15				
		15	0.35	−23	0.64	—				
22	X	0			1.89	−27	0.31	+58	0.45	−45
		15			1.89	−16	0.25	+24	0.32	−23
	Z	0	0.38	−13	1.40	−27	0.12	—		
		15	0.41	−15	1.42	−15	0.12	—		

*Table II. Q, R, S, and T wave maximum amplitudes which occurred in 17 of the 24 patients. The amplitude values, in millivolts, are the means of 3 consecutive beats obtained from the recordings using electrodes with buffers. Percentage error is defined as the difference between the values obtained with and without buffers divided by the value obtained with buffers. Negative values indicate that the voltage without buffers is lower than that with buffers. Where no entries are shown, the wave either did not exist or the error was less than 0.05 mv. The patient numbers correspond to those in Table I.

Table II—Cont'd.

Patient N	Lead	Time (min.)	Q Amplitude (mv.)	Q % Diff	R Amplitude (mv.)	R % Diff	S Amplitude (mv.)	S % Diff	T Amplitude (mv.)	T % Diff
23	X	0			1 43	−31	0 05	+1 000	0 28	−150
		15			1 36	−13	0 05	—	0 33	− 27
	Y	0			1 83	−10			0 33	− 21
		15			1 80	− 7			0 40	− 12
	Z	0	0 58	−31	2 2	−39	0 20	—	0 27	− 41
		15	0 57	−11	2 2	−16	0 185	—	0 40	− 23
24	X	0			0 67	−70			0 22	− 73
		15			0 67	−16			0 23	− 22
	Z	0	0 22	−55					0 13	—
		15	0 20	—					0 14	—

cannot be constant because of their dependence on both frequency and current intensity.* Measurements made at our laboratory using electrodes as described have shown that skin to electrode impedances vary to only a minor extent when the current through the electrodes is varied over the range of 2 to 60 microamperes. However, they increase to remarkably high values when measured at frequencies in the neighborhood of 1 Hz because of the increased capacitive effects.

Results of many measurements showed that values for R, R_s, and C at 1 Hz (Fig. 4) of 30 K, 90 K, and 0.5 μf are not uncommon. Fig. 5 shows how the magnitude and phase angle of this impedance varies as a function of frequency. The data shown were taken from a single subject. The effect that this type of impedance might have on the measurement of ECG potentials could be both in the magnitude and phase shift. For those very low frequencies where phase angle is close to zero, the measured potentials will suffer primarily from amplitude distortion. T wave frequencies could be considered to be in this range, for example. At frequencies higher than 5 Hz, the capacitive effect of the impedance can cause phase shift distortions as well. Obviously, these distortions will depend on the value of the input impedance of the recording instrument as well as on the precise impedance versus frequency characteristics of the specific electrode sites involved. In many instances, for example, the capacitive component of the impedance is still quite substantial at very low frequencies, yielding phase angles of about 30 degrees at 1 Hz.

For the patients of this study, skin impedance values were measured at a sine wave frequency of 10 Hz. This frequency was selected because of its being representative of the fundamental frequency of the QRS complex, although there is often a sizable capacitive component active at this frequency. In any event, this permitted a simple measurement technique yielding values that can be compared from subject to subject. Obviously, measurements at this frequency alone do not reveal, except in a very general way, the impedance values at frequencies in the 0.05 to 5 Hz range which are of great importance in determining T wave and ST segment distortions.

Electrode buffer amplifiers and ECG recordings (Frank system). The use of weighting networks, such as the Frank network, used in this study will usually lead to an effective R_s (Fig. 6) that will make the effect of high skin to electrode impedance values of great importance. For these kinds of recordings, therefore

*These increased capacitive effects are probably due to a combination of the double layer and Faradaic leakage phenomena. The variation of electrode impedance with frequency has been thoroughly reviewed by Schwan.

buffer amplifiers for each electrode will permit more accurate potential measurements by minimizing the effect of the skin to electrode impedances. The high input impedance of the buffer permits the potential at its input to be largely unaffected by the skin to electrode impedance. The low output impedance of the buffer permits this undistorted potential to be applied across the input terminals of the weighting network.

The values of skin impedance listed in Table I for the 24 patients demonstrate the great variability in values obtained both on the same subject and from one subject to the next. There is no doubt that all these values could have been substantially reduced if the skin had been rubbed vigorously before application of the electrodes. In practice, however, this procedure is seldom followed rigorously and the values shown in this table are probably quite typical of what would be encountered in most ECG laboratories.

The variation in electrode to skin impedance with time seems difficult to explain. In most cases when the initial value was low, on the order of 5 K or less, the variation with time was either negligible or masked by the imprecision of the measurements. When the initial values were high, their tendency to decrease with time could probably be attributed to the combined effect of the penetration of the electrode paste through the subcutaneous skin layers and local sweating of the skin beneath the electrodes. In those smaller number of

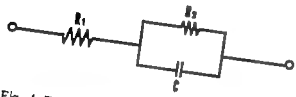

Fig. 4. Equivalent circuit of skin to electrode impedance as given by Geddes and Baker.

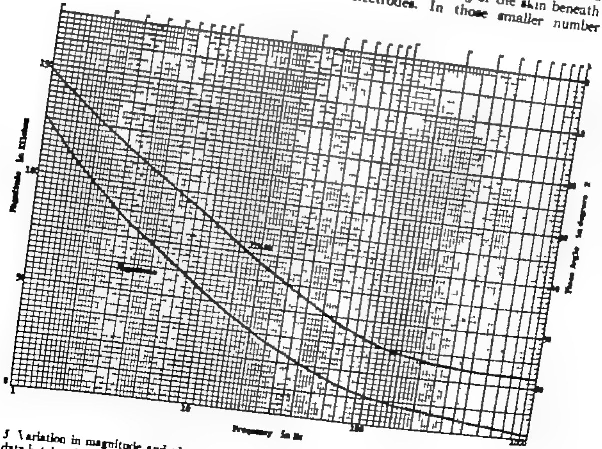

Fig. 5. Variation in magnitude and phase angle of skin to electrode impedance as function of frequency. The data is taken from a single subject to demonstrate a typical case.

cases where skin to electrode impedance increased with time, no simple explanation was evident.

The consistency noted in the low skin to electrode impedance values for the forehead electrode may be of some practical interest. This low impedance value is due in large part to the relatively thin layer of skin on the forehead as compared with the other electrode sites. Although this has not been tried here it is suggestive of the possibility of achieving better results using limb electrode locations on thin skin areas when possible. For example the arm electrodes could be placed on the ventral rather than the dorsal area of the forearm

Comparison of Tables I and II reveals that knowledge of the skin to electrode impedance values does not necessarily permit the prediction of ECG distortions. For example Patient 7 had high values for impedance at electrode locations E and F but no ECG differences were notable between recordings taken with and without buffers. On the other hand where skin to electrode impedance values were consistently low at each electrode site it was safe to predict that the ECG would be unaffected by recording without buffers.

Reference to Table II shows that R wave amplitude errors occurred more often than any other errors. In fact 29 of a total of

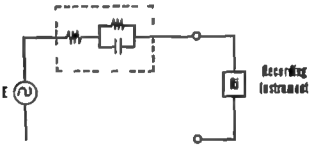

Fig. 6. Schematic showing cardiac potential *E*, skin to electrode impedance within dotted lines, and *Ri* representing the input impedance of the recording device.

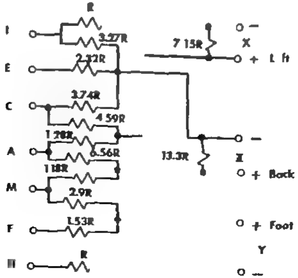

Fig. 7. Frank resistor network.

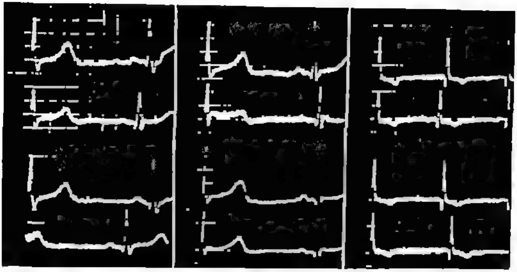

Fig. 8. Oscilloscope photographs of Frank leads of 3 different subjects. In each inset, the upper trace is the recording using buffers and the lower trace is the recording without buffers. Upper left, X lead at time zero. Lower left, Same lead 15 minutes later; vertical sensitivity 1 mv./3.5 divisions; horizontal sensitivity 100 ms/division. Upper middle, X lead at time zero. Lower middle, Same lead 15 minutes later; vertical sensitivity 1 mv./3.5 divisions; horizontal sensitivity 100 ms/division. Upper right, Z lead at time zero. Lower right, Same lead 15 minutes later; vertical sensitivity 1 mv./2.5 divisions; horizontal sensitivity 200 ms/division.

In all cases, note the higher amplitude obtained using buffers and its stability with respect to time. Note also the increase in amplitude which occurs with time when no buffers are used.

60 errors for the 17 patients were R wave errors. The number of T wave amplitude errors was 13. Only those errors greater than 0.05 mv. are listed. It should be noted that, although there is some convenience in showing it this way, expressing errors in percentages tends to make errors in low amplitudes appear more significant than those in high amplitudes. This certainly helps to account for the high percentage errors in T waves as compared to QRS waves.

The relative frequency of occurrence of errors in the X, Y, and Z leads can be somewhat explained on the basis of the makeup of the Frank resistor network (Fig. 7). Of the 3 electrodes contributing to the Y lead potential, one of them feeds directly into one side of the preamplifier through a resistor. Therefore, variations in the electrode to skin impedance at this site (H) will have no effect because of the high input impedance of the preamplifiers. The other 2 electrode potentials (F and M) add together to feed into the other side of the preamplifier. However, since the contribution of F is so much greater than that of M, skin to electrode impedance values at M will cause relatively small errors in the measured potentials. These facts account for the low frequency of occurrence of errors in Y, only 4 of the 24 patients showing such errors. In the cases of X and Z, the several electrodes contributing to these potentials are weighted more uniformly and this would account for the increased effect of skin to electrode impedance values on the measured potentials. Note that although the resistor network weighs C considerably less than A for the X lead, the contribution in potential from C is very important because of its proximity to the heart. This is in contrast to M for the Y lead. The photographs of Fig. 8 depict typical errors which are caused by electrode to skin impedances.

Electrode buffer amplifiers and standard ECG leads. Where strictly bipolar potentials are recorded as in standard Leads I, II, and III, it is sufficient to use preamplifiers with high input impedances to effectively eliminate distortions that could be caused by high electrode to skin impedance values.

Although the results presented above are based on the use of the Frank leads,

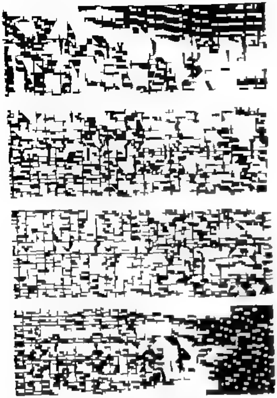

Fig. 9. Direct-writer tracings of a single subject at 25 mm. per second paper speed. Upper tracing is aVR recorded conventionally without buffers. Below it is aVR recorded using buffers. The third and last tracings are V recorded without and with buffers, respectively. Note the decreased amplitude in both leads when buffers are used. See text for explanation.

there is no doubt that comparable errors may be present when using other weighting networks, as in the Wilson central terminal. In the recording of the standard chest leads, the central terminal is formed by the common connection of 3 equal resistors whose other ends are attached to the right arm, left arm, and left leg electrodes. The intention is to form a terminal that is equally weighted by the 3 potentials at these electrodes. This weighting can be profoundly altered when high skin to electrode impedances exist at any of these sites. In many existing direct writers, the resistor values are on the order of 10 000 ohms. If, for example, the skin to electrode impedances were negligible at LA and LL, but was 10 000 ohms at RA, the central terminal potential would be (assuming infinite input impedance for the preamplifier) $\frac{2\ LA}{5} + \frac{2\ LL}{5} + \frac{RA}{5}$ instead of the intended $\frac{LA}{3} + \frac{LL}{3} + \frac{RA}{3}$. Similar problems would be encountered in the recording of the augmented leads.

A number of subjects were used to test the effect of skin to electrode impedance on conventional lead ECG's. Recordings were made on each subject without removing electrodes. For one set of recordings, buffers were inserted in each of the RA, LA, LL, and chest electrodes. Of 7 subjects, 5 showed differences in at least one of the leads which were caused mainly by the inaccuracy of the central terminal potential as described above. Fig. 9 is an example of the kinds of errors that can occur in the standard leads. The direct writer used in these recordings is a commonly used commercially built unit having the central terminal formed with 10 K resistors.

It is interesting to note in Fig. 9 that amplitudes were somewhat lower when buffers were used. There is a reasonable explanation for this. If the central terminal amplitude is reduced by an increased skin to electrode impedance at an electrode contributing to this potential, for example, the recorded potential may be increased since what is actually being recorded is the difference between the potentials of exploring electrode and central terminal. In general, the change in amplitudes caused by skin to electrode impedances may go either way depending on which electrodes are involved and to what extent.

The advantages of recording the unipolar limb leads with buffer amplifiers has been noted previously by Dower[1] and Schwarzschild and associates.[11]

Buffer characteristics. Of the 24 patients studied, the highest encountered value of skin impedance at 10 Hz was 206 K. Although this was not "typical," it is to be expected that values close to this would not be uncommon at frequencies in the range of 1 Hz since, as noted earlier, impedance increases drastically as frequency decreases. Although the buffers used in this study had input impedances of about 3 megohms, a value closer to 10 megohms

would be more appropriate. For example a 200 K skin to electrode impedance would result in an amplitude error on the order of 10 per cent when used with a buffer input impedance of 2 megohms. A 10 megohm input impedance would reduce the error to about 2 per cent. It is especially important that this high value of input impedance be maintained for the buffer at low frequencies (below 10 Hz).

One other aspect of the use of the buffer deserves mention. In order to fulfill its function of minimizing the effect of skin to electrode impedance, the buffer must be placed between the electrode and the weighting network. In the study presented here, the buffers were located close to the electrodes; however, they could just as well be located at the other end of the patient cable in the recording equipment. One advantage of placing them in close proximity to the electrodes is that electromagnetic pickup in the patient cable will be reduced because of the low output impedance presented by the buffers. There is some convenience in placing the buffers within the equipment. If this is done, the use of shielded leads for the patient cable may cause undesired effects due to the capacitance of the leads. These capacitance effects may be effectively eliminated by judicious design of the buffers so as to present a negative input capacitance to neutralize the effect of the patient cable.

Finally, it should be noted that the design of an adequate buffer has become relatively simple and inexpensive because of the commercially available integrated circuit components.

Summary

The effects of skin to electrode impedance on ECG potentials were determined by recording Frank leads with and without buffer amplifiers on 24 patients over a 15-minute period. Recordings were taken every 5 minutes without moving the electrodes in order to study the effects as a function of time. Electrode to skin resistance was measured every 5 minutes at each electrode site. The results demonstrated that skin to electrode impedance values were extremely variable and unpredictable, ranging between 0 and 206 K at 10 Hz. In most instances they decreased with time. Errors in Q, R, S, and T wave amplitudes, measured using a digital computer, occurred in 17 of the 24 patients as a result of skin to electrode impedances. These errors were effectively minimized when buffer amplifiers at each electrode were used. It is recommended that buffer amplifiers having at least 10 megohms input impedance at low frequencies be employed in ECG recording whenever weighting networks are used between the electrodes and the recording device.

In the use of standard leads with present day direct writers, it has been demonstrated that skin to electrode impedances may produce amplitude errors in the recorded potentials, especially in those leads which require the use of a central terminal. Buffer amplifiers, when used for the limb electrodes, will effectively prevent such errors in the recording of conventional precordial and augmented leads.

REFERENCES

1. Schmitt, O. H., Okajima, M., and Blaug, M.: Skin preparation and electrocardiographic lead impedance, Digest of 1961 International Conference on Medical Electronics, p. 236.
2. Frank, E.: An accurate, clinically practical system for spatial vectorcardiography, Circulation 13:737, 1956.
3. Schmitt, O. H.: Averaging techniques employing several simultaneous physiological variables, Ann. New York Acad. Sc. 115:952, 1964.
4. Spach, M. S., Barr, R. C., Havstad, J. W., and Long, E. C.: Skin-electrode impedance and its effect on recording cardiac potentials, Circulation 34:649, 1966.
5. Pipberger, H. V., Baule, G., Berson, A. S., Briller, S. A., Geselowitz, D. B., Horan, L. G., and Schmitt, O. H.: Recommendations for standardization of instruments in electrocardiography and vectorcardiography. Report of subcommittee on instrumentation, committee on electrocardiography, American Heart Association, IEEE Trans. Biomed. Eng. BME 14:60, 1967.
6. Kossmann, C. E., Brody, D. A., Burch, G. E., Hecht, H. H., Johnston, F. D., Kay, C., Lepeschkin, E., and Pipberger, H. V., and Subcommittee on Instrumentation: Pipberger, H. V., Baule, G., Berson, A. S., Briller, S. A., Geselowitz, D. B., Horan, L. G., and Schmitt, O. H.: Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Report of committee on electrocardiography, American Heart Association, Circulation 35:583, 1967.
7. Talack, L., Marden, E., Mason, H. L., and

Pipberger H V Digital recording of electrocardiographic data for analysis by digital computer IRE Trans. Med. Electronics ME-6 167 1959

8. Geddes, L A., and Baker L. E. The relationship between input impedance and electrode area in recording the ECG, Med. Biol Eng 4:439 1966.
9. Schwan, H. P Determination of biological impedances Physical techniques in biological research, New York and London, 1963 Academic Press, Inc., page 323
10. Dower G. E. Some instrumental errors in electrocardiography Circulation 28:483, 1963.
11. Schwarzschild, M M Hoffman, I and Kissin, M Errors in unipolar limb leads caused by unbalanced skin resistances, and device for their elimination Am. Heart J 48:235 1954.

Appendix

The skin to electrode impedance was determined at 10 Hz assuming its value to be mainly resistive in nature. In a small number of measurements where a significant phase shift was observed a suitable correction was made to determine the magnitude of the impedance. As shown in Fig. 3 the applied voltage of 1 volt at 10 Hz was used to provide a current flow through 2 electrodes. Using a known resistor R the current was adjusted to a value between 10 and 60 microamperes.

The value of R_1 plus R_2 could then be calculated as

$$R_1 + R + R = \frac{E_{in}}{I}$$

$$(R + R_2) = \frac{E_{in}}{I} - R$$

$$\text{where } I = \frac{V}{R}$$

In order to determine the values of R_1 and R separately at least 3 measurements must be made using 3 electrodes. Thus $(R_1 + R_2)$ may be found as above $(R_1 + R_3)$ may be found using electrodes 1 and 3 and $(R + R_3)$ may be found using electrodes 2 and 3 Three simultaneous equations may then be solved to obtain R_1 R and R_3 separately

In the determination of electrode to skin resistance values therefore 7 separate, i.e., independent, measurements must be taken between pairs of electrodes.

Electrode polarization effects at 10 Hz were ignored after a small number of measurements revealed no significant polarization potentials at this frequency

Case reports

Pulmonic stenosis caused by a malignant tumor of the heart

A case report

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Acquired pulmonic stenosis is among the rare disorders of the heart. The causes mentioned in the literature are reviewed in a publication by Babcock and associates.[1] Tumors arising from the heart or localized near its base can produce such a stenosis. This paper describes a female patient with a sarcoma of the heart and pulmonic stenosis, diagnosed during life on the basis of an exhaustive examination.

Case report

The patient was a 38-year-old nurse with symptoms dating back to 1963 when she repeatedly had a sensation of fainting during a hike in the mountains. Later she noticed occasional acceleration of the heartbeat in association with fatigue. During that period she developed dyspnea at moderate exertion, e.g., walking upstairs. In view of these relatively unimportant symptoms, she consulted her physician. A systolic murmur was heard and she was given a cardiological examination.

At that time, the pulse was regular. The blood pressure was 115/80 mm. Hg recumbent as well as standing. A systolic murmur was audible at the heart, with maximum intensity in the second and third intercostal spaces to the left of the sternum, with some conduction to the back. The heart sounds were normal. Routine laboratory findings were normal.

The electrocardiogram (ECG) showed a sinus rhythm, normal conduction times, and a vertical position of the heart axis. There was an S in V but no other indication of hypertrophy of the right ventricle.

X-ray examination disclosed a rather large heart with an effaced waistline. In the right oblique projection some slight bulging of the conus arteriosus was seen. In the left-oblique projection the configuration of the heart was normal.

Phonocardiography disclosed a holosystolic diamond-shaped murmur with a late systolic maximum. The amplitude was small. The punctum maximum was localized over the third intercostal space to the left of the sternum. The pulmonary component of the second sound was virtually invisible. The carotid pulse tracing was normal, as was the left atrium tracing. The venous pulse was normal apart from a slightly high A wave.

At heart catheterization in March, 1964, linear oxygen saturations were found in the right heart. The oxygen saturation of the radial artery was 95 per cent. The pressure in the right atrium averaged 2 mm. Hg. Right ventricle inflow tract 66/2, outflow tract 42/2, pulmonary artery 42/6, peripheral segment 8 mm. Hg. This meant a fall of pressure in the outflow tract of the right ventricle by 26 mm. Hg at rest (Fig. 1).

The patient was discharged with a diagnosis of infundibular pulmonary stenosis of relatively little hemodynamic significance and resumed work. In the autumn of 1964 the symptoms gradually progressed to distinct dyspnea at the slightest exertion,

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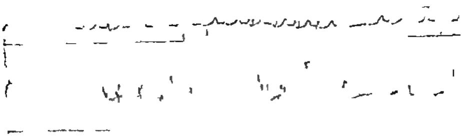

Fig. 1 Heart catheterization, March, 1964; withdrawal tracing from pulmonary artery to right entricle

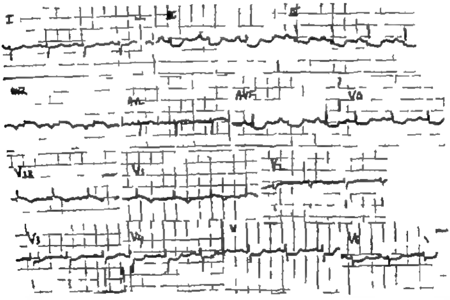

Fig 2 Ele rocardiogram, June, 1965

with ttacks of dyspnea also t rest. Cyanosis gradually became apparent also. By the end of 1964 the patient began to suffer from presternal pain, radiating to the back.

I February 1965 the patient developed fever hich lasted few days, and the symptoms increased. She was hospitalized in Austria, where she was orking at the time. The blood pressure was 100/60 mm. Hg and -rays disclosed nequivocal enlargement of the heart. The temperature had returned to normal. Pericardial friction rub was udible on the fourth day The erythrocyte sedimentation rate (ESR) was 74 to 115 mm. after 1 and 2 hours, respectively The antistreptolysin titer (AST) was normal 220 U Pericarditis was diag nosed. Antibiotics, and later prednisone seemed to lead t improvement. After month, however the condition obviously deteriorated. The patient complained of severe dorsal pain and the dyspnea increased I M y she was taken t the Netherlands.

The patient was admitted to our department on June 1 1965 The predominant symptom was pain in the back at the level of the scapulae and often simultaneously in the anterior aspect of the thorax. The pain was sometimes localized on the inside of the right upper arm, or occasionally in the left arm. There was no radiation to the cervical region. The pain was independent of respiration but learly correlated to the position of the body in particular there was aggravation when the patient was lying on the left side she was unable to sit up straight for any length of time The pain was least severe hen she was lying on the right side Oxygen inhalation alleviated the pain. Any exertion produced dyspnea, but spontaneou attacks of dyspnea had ceased. The patient did not cough. There as no dysphagia and no hoarseness, no ttacks of dizziness, nd no tendency to collapse.

Examining this patient, w saw a woman in good nutritional ondition and with intact mental faculties. There was nmistakable cyanosis of the skin and mucosa but the fingers were not clubbed. The

pulse was regular at rate of 90 beats per minute. The blood pressure (upper arm) was 120/70 mm. Hg The veins the cervical region showed moderate overfilling A brief) tolic m rmur wa ud'ble over the cervical region. The carotid arterial pulsations were normal. The thorax was symmetrical, part from a slightly more pronounced curvature to the left tha to the right of the sternum The pex beat was felt n the midclavicula line The heart sounds were normal, with rather loud first sound at the pex. There was a systolic murmur with maximum intensity from the first to third ribs to the left of the sternum, nd much less distinct over the apex. I the lateral recumbent position, possible diastolic murmur was heard over the apex. Percussion and auscultation of the lungs revealed no abnormality The liver did not seem to be enlarged and no edema was found The peripheral arterial pulses were intact. The spine nd limbs showed normal mobility Palpation and percussion elicited pain nowhere. Further physical findings were all normal.

Laboratory finding Blood tests revealed hemoglobin concentration of 15 1 Gm per 100 ml. 4.3 million erythrocytes per cubic millimeter 14 700 leukocytes per cubic mill meter (with differential cou t of 2 eosinophils, 1 staph cell, 73 segmented cells 17 lymphocytes, and 7 monocytes) and an ESR of 17 mm. after 1 hour and 30 mm fter 2 hours. The concentration of rea was 0.22 Gm. per liter of creatinine 8 0 mg per liter and of bilirubi 5 4 mg per liter The thymol turbid'ty was 1 2 U nd the alkaline phosphatase was 195 μmole per minute per l ter Enzyme activities were as follows serum glutamic oxalacetic transaminase (SGOT), 16 U serum glutamic pyruvic transaminase (SGPT), 17 U lactic dehydrogenase (LDH), 290 U β-hydroxybutyrat dehydrogenase (HBDH) 202 U creatine phosphokinase (CPK) 0 U The total protei value was 8 0 Gm. per liter with fractions as follow albumin 55 per cent α_2-globulin 11 per cent β-globulin, 12 per cent γ-globuli 15 per cent. Th glucose concentration was 1 10 Gm per liter

Test of the urine revealed the following findings Albumi egati e, glucose neg ti urobilin trace, bilirubin negati o sporadic leukocytes in the sed ment.

The ECG (Fig 2) showed a sinus rhythm (100 per minut), AV interval 0 16 sec QRS width 0 06 sec vertical position electrical xis. There was prominent P wa i Lead II high R in aV RsR' in V_{3R} and V S o far as V ST depression i Leads II III aV V_4, and V through V

Radiological findings The lung fields were clear without infiltrative cha ges The vascular pattern in the right l ng seemed diminished (Fig 3). I the anteroposterior (AP) projection th heart shadow showed a large bulge t the sit of the conus arteriosus. The right heart contour lso bulged. The right oblique projection showed an excurs tion of the posterior aspect mmediately abov the diaphragm. The left atrium did not seem dilated. The bulge t the side of the conus arteriosus projected entrally here The left oblique projection disclosed bilateral broadening of the heart, but with normal contours.

At phonocardiography (Fig 4), e recorded normal first sound followed immediately by diamond-shaped murmur with a late maximum the decrescendo of which overlapped the second ortic sound The murmur was most pronounced on 2L1 No jection sound was udible a ywhere. A small pulmonic sound occurred 0 14 second after the second aortic sound. A low frequency trial sound occurred on 4L1 The carotid pulse tracing as normal, with prominent dicrotic The upstroke time of the femoral artery pulse tracing was 0 10 second The venous pulse tracing showed a narrow x descent. In the lateral recumbent position, a few pulsation curves of normal aspect were recorded long the left sternal border The ejection time measured from the carotid pulse tracing as 83 per cent

I iew of these data, and especially because of

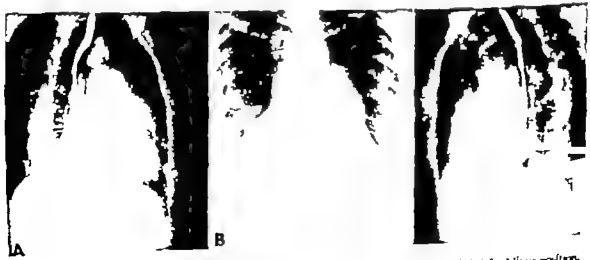

Fig 3 X-rays, June 1965 A Right oblique position, B posteroanterior direction nd C, left oblique position.

the electrocardiographic evidence of right ventricular strain, it was assumed that the pulmonary stenosis had rapidly increased i severity and that, in ddition, right-to-left shunt had developed—probably t an trial level through patent foramen ovale or an trial septal defect overlooked t the first heart catheterization. The probable aggravation of the stenosis in conjunction with the abnormal x-ray findings, seemed t suggest tumor growth in the outflow tract of the right ventricle. I order t achiev maximum certainty in ruling out reversible abnormality heart catheterization as carried out in combination w th angiocardiography

Low oxygen values were found in the right heart. The catheter (introduced via the right great saphenous vei) could be passed int the left atrium through the trial septum. I the left trium, and also in pulmonary ein, normal oxygen saturation was found. The saturation in the femoral artery proved to be greatly diminished. The saturation and pressure alues found are shown in Table I The ithdrawal curve from the left pulmonary artery to the right entricle show two systolic pressure increases one of 26 mm. Hg in the trunk of the pulmonary artery and another of 32 mm. Hg in the outflow tract of the right ventricle (Fig 5). It was impossible to reach the right pulmonary artery The pressure curve of the right entricle disclosed mechanical alternation. The diastolic pressure was slightly increased. The right trial

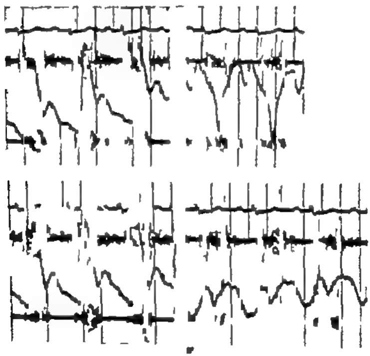

Fig 4 Phonocardiogram J ne, 1965 Above, left, carotid tracing with sound tracing abov the pulmonary area above, right, enous tracing with sound tracing same area Below left, carotid tracing with sound tracing below left clavicular bone below right, pulse tracing taken over hepatic area with sound tracing at left lower sternal border

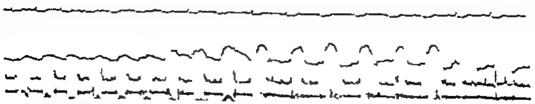

Fig. 5 Heart catheterization, J ne 10 1965 ithdra al tracing from lef pulmonary artery to right heart chamber ECG, pressure curve and intracardiac phonocardiogram.

curve showed increased pressure deep y descent was seen.

At cineangiocardiography contrast medium i jected to the superior vena ca wa seen t flow to the left heart t the level of the tri m Some filling defects were visible the trunk of the pul monary artery Especially the left oblique projection the trunk showed a distinctly reduced diameter The right pulmonary artery did not fill only trace of contrast medium was visible at the begin ing of this vessel. The left heart hadow originally mistaken for the conus arteriosus extended far laterally beyond th limits of the contrast medium The left mai branch seemed slightly dilated. From the left trium, the left ventricle and aorta filled i the normal manner (Fig 6).

The data obtained by heart catheterization nd angiocardiography indic ted occlusion of the right pulmonary artery—a supravalvular and infundibular tenosis—caused by an expanding process the heart shadow showed extraluminal expansion to the left t the lte of the onus arteriosus, and a right to left shunt existed t atrial level

On the basis of these f ndings, we diagnosed a maligna t tumor of the heart chiefly affecting th outflow tract of the right entricle and lso in ading the pulmonary artery

The patient condition remained nchanged til the sudden death on J ne 15 1965

Postmortem findings The mediastinum contained a tumor the size of cocon t, growing from th heart. The heart with the tumor weighed total of 1 150 grams. Tumor tissue covered two-thirds of the heart surface and large nodular mass had formed, mainly t the site of the conus arteriosus Here, the tumor had penetrated the muscular wall of the right ventricle, causing stenosis of the in f nd bulum (Fig 7) Th tumor had also nvaded the wall of the pulmonary artery constricting this artery to a mere crevice (Fig 8). The intra-arterial tumor follow the course of this artery nd beyond the bifurcation causes complete obstruction of the right pulmonary artery Between the greatly dilated right atrium and the normal left trium the foramen ovale is wide open (th diameter of the round opening is 1 cm). The right ventricle show marked hypertrophy nd its muscular w ll is 1.3 cm thick. The wall of the left ventricle is of normal thickness. The aortic val es are intact, as is the aorta although this vessel is completely enveloped in tumor tissue.

The microscopy of the tumor is that of poly morphous round cell sarcoma with extensi necrosis (Fig 9).

Both the li er and the spleen are enlarged (weights of 1,800 nd 190 grams, respectively) and microscopically both show congestion. N metastases are t be found

Discussion

I rimary tumors of the heart are known to be rare Cases reported in the literature are reviewed in a few publications.[1-4] The diagnosis is impeded by the frequent absence of clinical symptoms or the lack of specific symptoms. A tumor localized in or near a heart valve can produce symptoms of stenosis or insufficiency of the

Table I Data of heart catheterization Oct 6 1965

Situation of catheter tip	Oxygen saturation (per cent)	Pressure (mm Hg)
Vena cava inferior	46 5	—
Vena cava superior	44 40	—
Right atrium	43	10/6
Right entricle	42	86/4/12
Right ventricle outflow tract	—	54/8/14
Pulmonary artery trunk	35	50/20
Left pulmonary artery	—	28/17
Vena pulmonalis	99	—
Left atrium	96 5	10/6
Left ventricle	—	72/0/4
Femoral artery	77	—

Fig. 6 Angiocardiogram J ne 10 1965 ont ast i jection in superior vena cava, l-A position.

Fig. 7. Cross-section through the heart with right ventricle (R.V.), outflow tract (OT), and just visible pulmonary valves. The outflow tract is narrowed and surrounded by tumor tissue (T).

Fig. 8. The pulmonary bifurcation has been opened: the right pulmonary artery is obliterated by tumor tissue.

Fig. 9. Microscopical view of the tumor: The tumor invading the myocardial muscle fibers.

valve in question Of the malignant heart tumors described a number have been localized in the outflow tract of the right ventricle or in the pulmonary artery In these cases the diagnosis was generally not made before autopsy [7, 11] A number of these tumors seemed to grow from the wall of the pulmonary artery

In the course of subsequent years improved diagnosis with the aid of heart catheterization and angiocardiography made it possible to detect a few cases of such tumors with pulmonary stenosis in living patients [22, 23] In the case described by Pund and associates [?] the diagnosis was established on the basis of a cytological study of pericardial and pleural fluid

In the woman described in this report the tumor initially manifested itself (at a cardiological study made elsewhere) as an isolated infundibular pulmonary stenosis In the terminal stage of illness hemodynamic data in addition demonstrated a supravalvular pulmonic stenosis and a right to left shunt at an atrial level Angiocardiography disclosed filling defects caused by tumor growth and confirmed the diagnosis.

The records of the pathological institute proved to include two other reports on primary sarcomas of the heart which also had caused stenosis of the pulmonary artery In view of the paucity of clinical data, it is our intention to discuss the pathological anatomical findings in these cases in another publication

Pathologists have pointed out the existence of benign tumors of the pulmonary valves, many of which are unimportant from a hemodynamic point of view Catton and co-workers,[25] however described a case of severe pulmonic stenosis caused by a myxoma diagnosed on the basis of angiocardiographic findings. Of the benign tumors growing from the right ventricular wall we would like to mention rhabdomyomas which are usually localized in the septum and can produce an infundibular form of pulmonic stenosis these tumors too may remain unimportant from a clinical point of view Angiocardiographic studies have proved useful in these cases also.[26] There are likewise some reports on myxomas arising from the right ventricular wall [27-30] A critical review of the further pertinent literature has been made by Sakakibara and associates.[31]

Clinical identification of benign tumors is of evident importance with a view to developments in cardiac operation Extra cardiac tumors can cause pulmonic stenosis by compression [1, 32-34] In a number of cases, this has been diagnosed in living patients. [35-38]

Summary

A description is given of a case of primary sarcoma growing from the right ventricular wall of the heart with stenosis of the pulmonary artery as a result of invading tumor tissue Two other cases are mentioned

In the case described the initial manifestation suggested an isolated infundibular pulmonic stenosis. A right to left shunt through a patent foramen ovale developed later

The diagnosis was established by angiocardiography during the patient s life.

The authors are indebted t J F Visser M.D cardiologist t Enschede for suppl ing the infor mation and records of the first heart catheterization

REFERENCES

1 Babcock, K B Bookstein J J and Judge R. D Acq ired pulmonic stenosis, Circulation 26:931 1962.
2. Straus, R nd Merliss, R Primary tumor of the heart Arch P th 39 74 1945
3 Mahaim I Les tumeurs t les pol pes du coeur Etude anatomoclinique, Paris, 1945, Masson et Cie
4 Whorton, C M Cancer 2:245, 1949
5 Prichard, R. W T mors of the heart, Arch P th. 51:98, 1951
6 Meyer A. H and Herschel, J G Een patient met een primaire harttumor Ned. Militair Geneesk tijdschr 18:337 1965.
7 Dean, G., nd Falconer A W Primary tumors of the valves of the heart, J Path. & Bact. 18:64 1913.
8. Rehder H Ein Beitrag zur Kenntnis des sogenannten Rhabomyoma des Herzens, Vir chows Arch. 217 174 1914
9 Mandelstamm, M Ueber primäre Neubil dungen des Herzens, Virchow Arch. f. Path Anat. & Physiol. 245:43, 1923
10. Eschbach, H Ueber ein malignes Leiomyom des Endocards m t Verstopfung der Lungen schlagader Zieglers Beiträge f P thol Anat z. Alg P th. 80:672, 1928
11 Froboese, C. Emboliformes Sarkom des Haupt stammes der Pulmonalarterie Zentralblatt f Alg P thol. & Anat. 44 148, 1928-1929.

12. Kadlech, H., and Schuh, W. Ein Beitrage zum myoplastischen Sarkom der Lungen schlagader Virchows Arch. 294:113 1935
13. Goedel, A. Zur Kenntnis des primären Lungenschlagader Sarkoms, Frankfurter Ztschr Path. 49:1 1936.
14. Martin, W. C., Techy, E. L., and Will, C. Primary tumor of the heart (entrance of the pulmonary artery) Am. Heart J 17 728, 1939
15. Heythorn, S. R., Ray, W. B., and Wolff, R. A. Primary fibromyxosarcomas of the heart and pulmonary artery Am. J Path 17:261 1941
16. Shelburne, P. A. Primary sarcoma of the heart, Ann. Int. Med. 29 1139 1948.
17. Mannix, E. P. J. and Lukash, L. Primary rhabdomyosarcoma of heart producing marked obstruction of pulmonary valve, Bull. St Francis Hosp. (Roslyn) 15 14, 1958.
18. Hagström, L. Malignant mesenchymoma in pulmonary artery and right ventricle Acta path. microbiol scandinav 51:87 1961
19. Blum, H. Fall eines malignen primären Herztumors, Ther Umsch. 18:50, 1961 cited by Hallermann, J.A.M.A. 148:939 1963
20. Fanconi, G. Tumoren des Herzens, die eine carditis rheumatica vortauschen, Helvet. paediat. acta 18:170, 1963
21. Reed Green, J. J. Crevasse, L. E., and Shanklin, D. R. Fibromyxosarcoma of the pulmonary artery, Am. J Cardiol. 13:547 1964.
22. Mannix, E. P. J. and Lukash, L. Primary rhabdomyosarcoma of the heart producing marked obstruction of the pulmonary valve, Bull. St Francis Hosp. 16:14 1958.
23. Hallermann, F J Mincad, O W Brown, A. L. cited by Pund[24] and Daugherty G W Rhabdomyosarcoma of the heart producing right ventricular outflow obstruction, J A M A 184:939 1963.
24. Pund, E. F Collins, T M Cunningham, J. E., and Hayes, J. R Primary cardiac rhabdomyosarcoma presenting as pulmonary stenosis, Am. J Cardiol. 12:249 1963.
25. Catton, R. W. Cratzeroth, W. G., and Reichenbach, D. D. A myxoma of the pulmonary valve causing severe stenosis in infancy Am. Heart J 66:248, 1963.
26. Taber R. E., and Lam, C. R Diagnosis and surgical treatment of intracardiac myxoma and rhabdomyoma, J Thoracic & Cardiovas. Surg 10:337 1960.
27. Kishimoto, M and Sakaibori, S. Primary tumor of the heart: report of case with myxofibroma of the right ventricle, Am. Heart J 57 769 1959
28. Gottsegen, G Wessely J Arvay A., and Temesvári, A. Right ventricular myxoma simulating pulmonic stenosis, Circulation 27:95 1963
29. Doohen, D J Green J W Diorio, A and Timmes, J J Emergency excision of myxoma of the right ventricle which was obstructing the right ventricular outflow tract J Thoracic & Cardiovas. Surg 4 :342, 1964
30. Sakakibara, S. et al. Myxoma of the right ventricle of the heart, Am. Heart J 69:382 1965
31. Joël, J Ein teratom auf der Arteria pulmonalis innerhalb des Herzbeutels, Virchows Arch. 122:381 1890
32. Rusby N L. Dermoid cysts and teratomata of the mediastinum review J Thoracic Surg 13 169 1944
33. Maier H. C Dermoid cysts and teratomas of the mediastinum with unusual features, Arch. Surg 67:154, 1948.
34. Kirakower C. A., and Gottsman, N J Clinical pathologic conference, Am Heart J 69:263, 1965.
35. Fry W Klein, C L., and Barton, H C. Malignant mediastinal teratoma simulating cardiovascular disease Dis. Chest 27:537 1955.
36. Wood, P Diseases of the heart and circulation Philadelphia, 1956 J B Lippincott Company p 689
37. Winter B Pulmonic stenosis produced by compression of the heart by an anterior mediastinal tumor Am Heart J 55 18, 1958.
38. Waldhausen, J A., Lombardo, C R., and Morrow A. G Pulmonic stenosis due to compression of the pulmonary artery by an intrapericardial tumor J Thoracic Surg 37:679 1959
39. Carney E Oppelt, W W Clewson, W L., and Brindley C O Cardiac Hodgkin's disease, Am Heart J 64 106, 1962
40. Shaver V C Bailey W H and Marrangoni, A. G. Acquired pulmonic stenosis due to external cardiac compression, Am J Cardiol. 16:256, 1965.

Intestinal obstruction caused by anticoagulants

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The differential diagnosis of acute abdominal conditions is often difficult. In particular, when one is dealing with intestinal obstruction, the etiologic possibilities are numerous. Frequently, even after all available laboratory tests have been exhausted, the diagnosis remains obscure. The use of anticoagulants, especially the prothrombin depressants, has introduced the iatrogenic syndrome of intestinal obstruction occurring secondarily to intra-abdominal hemorrhage.

With the ever increasing use of anticoagulant therapy, especially in the field of cardiovascular surgery, this cause of intestinal obstruction will be seen with increasing frequency. Although this is not a new entity, it remains unknown to many physicians today. It is especially important that the cardiologist and cardiovascular surgeon be keenly aware of this complication. Early recognition or, better yet, the prevention of this complication are as essential as proper management. For this reason, it is deemed worthwhile to report two such cases of this interesting entity and to review the findings and literature.

Case reports

Case 1. C. S., a 46-year-old man, was admitted to the Confederate Memorial Medical Center on Jan. 6, 1965, with a history of abdominal pain for 24 hours prior to admission. The pains were described as cramping in nature, at first periumbilical, later becoming localized to the right lower quadrant. He had vomited several times prior to admission with some relief. Sodium warfarin was started at the time of his first myocardial infarction in 1963 and continued after his last hospitalization for thrombophlebitis in December, 1964. The last prothrombin time prior to this admission was 39 secs. with a control of 12 secs. (10.5 per cent) on Dec. 30, 1964. At that time, it was recommended that sodium warfarin be continued at 5 mg. a day. Digitalis was the only other medication known to be taken by the patient.

Upon admission, the patient appeared acutely ill with a temperature of 100° F. and a pulse rate of 96. Examination of the abdomen revealed generalized tenderness with the right lower quadrant being acutely tender. Rebound tenderness was present. No masses were felt, and the bowel sounds were hypoactive.

The admission white blood count (WBC) was 13,159 with 80 segmented cells, 1 band cell, 13 lymphocytes, and 6 monocytes. Gross hematuria was present. The prothrombin time was 62 secs. with a control of 14 secs. (less than 10 per cent).

Acute abdominal x-rays upon admission revealed widening of the space between loops of bowel, which suggested free intraperitoneal fluid. An increased thickness of the bowel wall was noted in the region of the terminal ileum (Fig. 1).

The admitting diagnosis was acute appendicitis with possible rupture. Surgical exploration was carried out after correction of the prothrombin time with 60 mg. of phytonadione. Approximately 500 c.c. of blood was noted upon opening the abdominal cavity. The mesentery and bowel were noted to be bright red, edematous, and thickened 18 inches proximal to the ileocecal valve. Resection of a 10 inch segment was carried out. The pathologist reported thickening of the wall of the intestine with marked

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Fig. 1

Fig. 2

hemorrhage throughout the wall and mesentery. No thrombi were noted. The recovery was uneventful, and on the fourteenth postoperative day the patient was discharged on 2.5 mg. of sodium warfarin.

Case 2. M. H., a 72-year-old woman with a past history of chronic congestive failure and cerebral insufficiency, had been receiving sodium warfarin since Nov. 4, 1966. She came to the Confederate Memorial Medical Center on Dec. 5, 1966 with a four-day history of lower abdominal pains and pain in the left leg. A low-grade fever was first noted on the evening prior to admission. She described the pain as being colicky in nature and becoming progressively more severe each day. On the morning of admission anorexia and nausea developed, but vomiting did not occur. Digitalis was the only other medication known to be taken. On a clinic visit on Nov. 28, 1966, her prothrombin time was within the upper limits of good therapeutic control. Although she was advised to continue the drug at a dosage of 5 mg. every other day and 7.5 mg. on alternate days, she was never really stabilized on an appropriate maintenance dosage.

When seen in the admitting room on Dec. 5, 1966, she was having generalized abdominal pain, but was alert and in no acute distress. Her blood pressure was 150/90 with a pulse rate of 76. Generalized ecchymoses were present. Examination of the abdomen revealed generalized tenderness which seemed to be more severe in the right lower quadrant. The bowel sounds were described as hypoactive and there was no rebound tenderness. No masses were palpable. The femoral pulses were equal. A mild, superficial thrombophlebitis of the left calf was also noted.

The admission WBC was 10,067 with a normal differential. There was no hematuria or melena. Her prothrombin time was 101 secs. with a control of 14 secs. (less than 10 per cent).

Acute abdominal x-rays upon admission revealed scattered small bowel gas which was more pronounced in the lower portion of the ileum. A fluid level was seen in the cecum. It was the opinion of the radiologist, that this x-ray was suggestive of acute appendicitis or possibly mesenteric thrombosis (Fig. 2).

The admission diagnosis was partial small bowel obstruction due to intraperitoneal hemorrhage secondary to hypoprothrombinemia. Conservative management with nasogastric decompression, intravenous fluids, and 5 mg. of intravenous phytonadione was initiated. Phytonadione 10 mg. intramuscularly was ordered every 8 hours. Less than 24 hours after admission, the prothrombin time was 17 secs. with a control of 14 secs. (64 per cent activity). By this time the abdominal symptoms had subsided and the patient was tolerating a clear liquid diet. Her recovery was uneventful.

Discussion

Since the description of this complication of anticoagulant therapy in 195_ by Berman and Martinella, more than 50 cases have been reported. New case reports and articles on this entity in the recent literature[3] indicate its increasing clinical in-

Marfan's syndrome confined to the mitral valve region: Two cases in siblings

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Marfan's syndrome is a hereditable familial disease with frequent manifestations in siblings. However, some sporadic cases presumably derive from a *de novo* genetic mutation. An authoritative source on Marfan's syndrome, McKusick,[1] maintains that the reported estimate of sporadic cases is inordinately high in relationship to inherited cases. His experience indicates that no more than 15 per cent of all cases are derived by mutation, whereas other authors consider 70 per cent to occur by mutation. McKusick believes that the higher estimates result from incomplete family studies.

The two cases presented below support McKusick's contention, for if either case had been identified alone, it might have been considered as a *de novo* mutation. This occurrence of a forme fruste of Marfan's syndrome in siblings strongly favors a familial genetic defect. The siblings, both in the sixth decade, were studied at different hospitals within a period of 3 months. Neither patient demonstrated arachnodactyly, ocular abnormalities, or aortic involvement, which are considered to be the classic features of Marfan's syndrome.[1] Involvement of the cardiac valves, particularly the aortic and the mitral,[1] occasionally the tricuspid,[2] is less common but constitutes a recognized component of the syndrome and indeed may be the only manifestation of the disorder.[3]

Case reports

Case 1. A married woman, 55 years of age, had had a heart murmur since high-school days. She was essentially asymptomatic, except for edema and shortness of breath during her two pregnancies, until six years ago, when she noted dyspnea and palpitations. There was a normal sinus rhythm. Cardiomegaly, left ventricular heave, and a Grade IV systolic murmur at the apex and radiating to the axilla were found. She did well during the ensuing six years but one year ago noted easy fatigability. She subsequently developed rapidly progressing mitral insufficiency with regurgitation.

She was admitted to the Peter Bent Brigham Hospital for mitral valve replacement in 1967. This thin woman weighed 54 kilogram and measured 5 feet 4 inches ([illegible]) in height. Her preoperative blood pressure was 160/100 mm. Hg; the cardiac examination revealed a point of maximum impulse in the fifth left intercostal space, one half inch outside the midclavicular line, a left ventricular heave, and a systolic thrill at the apex. There was a pansystolic Grade V murmur at the apex which was heard throughout the chest. The radiologic examination demonstrated an enlarged heart with predominantly left atrial and ventricular enlargement.

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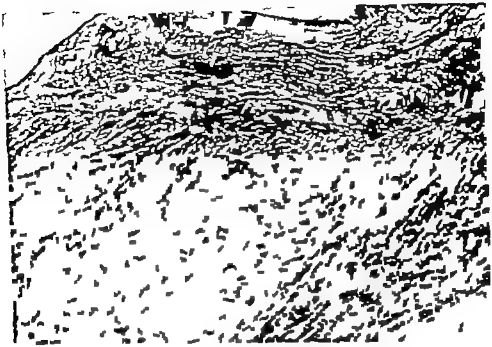

Fig. 1. Photomicrograph of mitral valve from Case 1 shows diffuse myxomatous change. The endocardial surface is at the superior edge of the photograph. Note the absence of inflammation or of vascularization. (Hematoxylin and eosin. × 40.)

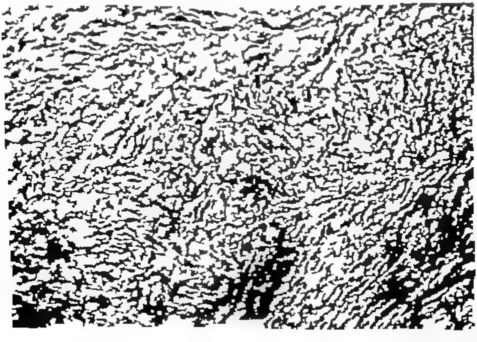

Fig. 2. Higher power view of myxomatous loose connective tissue seen in the mitral valve in Fig. 1. The mucopolysaccharide content of the myxomatous areas is increased and the elastic tissue is deficient. It is not surprising that this tissue is soft and the valve prolapses readily. (Hematoxylin and eosin. × 100.)

Fig. 3. Microcystic necrosis in mitral valve of Case 1 with basophilic staining of the cyst contents. This change is reminiscent of Erdheim cystic medial necrosis seen in the aorta in Marfan syndrome. Elastic tissue was deficient in the areas which had undergone cystic change. (Hematoxylin and eosin ×100.)

The lungs were clear. The pulmonary vascular pattern was normal and did not suggest mitral stenosis. There was no valvular calcification. Left ventricular cineangiography showed gross mitral insufficiency and no evidence of aortic insufficiency. At operation, a large flaccid friable insufficient mitral valve was noted. The aortic valve appeared normal. The mitral valve was replaced with a Harken disc valve.* The excised valve consisted of two soft thick leaflets without calcification. The specimen was received in two parts, one measuring 5.8 by 2.5 cm. and the other 3.6 by 1.6 cm. with a thickness of 0.3 cm. The normal valve thickness is 0.1 cm. Microscopically, the valve was thickened by collagenous relatively acellular tissue containing areas of basophilic and myxomatous change (Figs. 1 and 2). Elastic fibers were deficient. A few foci of microcyst formation were present in the basophilic areas (Fig. 3). The myxomatous alteration extended into chordae tendineae and adjacent muscle. There was no evidence of abnormal vascularization or endocarditis, healed or active. This patient had no past history suggestive of either rheumatic heart disease or other form of endocarditis. The patient did well initially after being discharged from the hospital, but four months after valve replacement she had symptoms indicative of recurrent mitral regurgitation presumably due to inadequate fixation of the prosthesis. In view of the loose myxomatous character of the tissue at the margins of the valve specimen, special procedures may be needed to ensure fixation in such cases.

Case 2. A 56-year-old Caucasian man, 5'5" tall and weighing 150 pounds, had a sudden onset of mitral regurgitation with congestive heart failure 3 months before his sister had her mitral valve replacement. Prior to this event, no cardiac murmur had been detected and there was no evidence of congenital heart disease, rheumatic, or any other form of endocarditis. Surgical exploration revealed rupture of chordae tendineae at the papillary muscle of the left ventricle. The soft noncalcified mitral valve was replaced. The surgical specimen consisted of a mitral valve with a circumference of 5.5 cm. and having two separate valve leaflets and a third slightly irregular disc of valvular tissue measuring 1.2 cm. in greatest diameter. The valve was almost twice the normal thickness with shortened, thick, and fused chordae tendineae running from one margin. There were two fragments of papillary muscle attached to two of the chordae. No calcium could be detected within the valve leaflets. Microscopically, the thickening was ascribed to dense collagenized fibrous tissue with small foci of basophilic change. There was no microcyst formation and only a minimal amount of myxomatous transformation. The chordae tendineae were thickened by collagenized tissue which extended into the papillary muscles with prominent fibrosis of the central portion of each papillary muscle. This patient has been able to resume his normal activities following cardiac operation.

*Surgery was performed by Dr. Dwight Harken.

Discussion

The history and body habitus of each family member was obtained. The parents of the two involved members had no stigmas to suggest Marfan's syndrome. None of their eight children shows overt manifestations of Marfan's syndrome. Five daughters, ranging in height from 5 4" to 5 7" had mesomorphic body habitus. Their two sons were 5 5" and 5 11" tall respectively. The two patients involved were the two youngest children. The two progeny of the female member with mitral insufficiency were 5 6" and 6 2" tall respectively. The taller of the two, a son, is slender and resembles his paternal grandfather who was also 6 2" tall.

The basic lesion consisting of collagenization with myxomatous change was present in the surgically removed valves from both patients with myxomatous change being more pronounced in the sister than in her brother. This change has previously been described as an isolated valvular lesion. The appearance of the mitral valve at the time of the operation usually renders it recognizable as a manifestation of Marfan's syndrome and has been termed the "floppy valve" syndrome.[4] Although calcification is usually not present in these valves it can occasionally occur and even ossification of the mitral annulus has been detected radiologically. Histologic examination assists in establishing the correct diagnosis. An increase in mucopolysaccharide content of the myxomatous portions along with microcyst formation and elastic tissue deficiency reminiscent of Erdheim's medial necrosis of the aorta are strongly suggestive of identification of the lesion with Marfan's syndrome. The connective tissue of the mitral valve annulus, leaflets, and chordae tendineae can be involved and the disease process may extend into adjacent papillary muscles and myocardium. Whenever a valve with these histologic features and lacking stigmas of rheumatic valvulitis is encountered Marfan's syndrome should be considered as the explanation for mitral insufficiency. The patients lack a history even suggestive of rheumatic fever in childhood although a murmur may have been detected in childhood. Of course rheumatic carditis is a far more prevalent cause of mitral regurgitation and can often be detected by a positive history, prolongation of the P-R interval, and T wave inversions in the electrocardiogram (ECG). Hypertrophic subaortic stenosis must also be considered in the differential diagnosis of acquired mitral regurgitation. Congenital causes must also be considered. Primary endocardial fibroelastosis would have a different histologic appearance with prominent increase rather than a deficiency of elastic tissue. Congestive heart failure usually has its onset in infancy in this disorder. Anomalous left coronary artery arising from a pulmonary artery can result in mitral regurgitation by producing dilatation of the mitral annulus. Endocardial cushion defects must also be considered.[6]

The diagnosis of spontaneous rupture of chordae tendineae can be made on the basis of severe mitral regurgitation associated with the sudden onset of cardiac symptoms, the abrupt appearance of an apical systolic murmur, and demonstration by radiography of a small left atrium. The abrupt worsening of symptoms of mitral regurgitation should also suggest the diagnosis of ruptured chordae tendineae. The vast majority of patients in this latter category have rheumatic valvulitis. However, in a recent review by Sanders and associates, 46 per cent of patients had no obvious cause for the rupture. Pathologic evidence of rheumatic involvement of the valve was lacking. Aortic regurgitation and hypertension might play a role in rupture of the chordae tendineae. Case described above identifies one of the lesions associated with Marfan's syndrome as a basis for rupture of the chordae tendineae.

Summary

The occurrence of mitral insufficiency as the sole manifestation of Marfan's syndrome in two siblings is supportive evidence for the genetic inheritance of this disorder as opposed to spontaneous mutation. The sister had a "floppy valve" with myxomatous transformation. The brother had rupture of chordae tendineae.

I am indebted to Dr. Benjamin Castleman, Massachusetts General Hospital, for permission to include Case 2, and also Dr. Pliney Allen for his cooperation in providing the history and body habitus of each family member.

REFERENCES

1. McKusick, V. A.: Heritable disorders of connective tissue, ed. 3, St. Louis, 1966, The C. V. Mosby Company.
2. Braunwald, E., and Wolfe, H. S.: Congestive heart failure in a 38-year-old woman with mitral insufficiency of twenty-five years' duration, Case Record No. 29-1967, New England J. Med. 277:92, 1967.
3. Segal, B., Kasparian, H., and Likoff, W.: Mitral regurgitation in a patient with Marfan syndrome, Dis. Chest 41:457, 1962.
4. Read, R. C., Thal, A. P., and Wendt, V. E.: Symptomatic valvular myxomatous transformation (floppy valve syndrome): Possible forme fruste of Marfan syndrome, Circulation 32:897, 1965.
5. Read, R. C., and Thal, A. P.: Surgical experience with myxomatous valvular transformation (floppy valve syndrome), Surgery 59:173, 1966.
6. Sanders, C. A., Austen, W. G., Harthorne, J. W., Dinsmore, R. E., and Scannell, J. G.: Mitral regurgitation secondary to ruptured chordae tendineae, New England J. Med. 267:943, 1967.

Clinical pathologic conference

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Clinical history

A 58-year-old man was admitted to the Medical College of Virginia Hospitals on May 17 1966, with complaints of pain in his chest, shoulder and back for two weeks The pain seemed to originate substernally and was described as being dull in character It was aggravated by coughing, but not by deep breathing H as unable to relate the pain to activity but he had noted dyspnea on exertion which had become progressively more severe. There was no orthopnea, paroxysmal nocturnal dyspnea, or dependent edema. Because of the progressive severity of the pain, he came to the hospital.

Past medical history revealed that the patient had had excision of ell-differentiated squamous cell epithelioma from the floor of his mouth in December 1963 with radical right neck dissection, tracheostomy and reconstruction of his mandible. The resected nodes and bones were free of tumor H received postoperative radiation therapy and returned t hav his tongue freed up in March 1964.

Review of systems was negative except as in the present illness.

Physical examination His temperature was 98.6 degrees, blood pressure 150/110, pulse 130, and respiration 20. The patient was well-developed, moderately plethoric man who ppeared uncomfortable but in no acute distress. A well-healed scar of the radical neck dissection was present with no evidence of recurrent tumor in the scar in adjacent tissue, or on the opposit side of the neck. His swallowing f nction was normal and the trachea as in midline. The optic fundi ere normal. The chest revealed dullness to percussion over the right base posteriorly and diminished breath sounds in the same region.

A few crepitant les were heard in both lung bases. The cardiac apical impulse was palpated 1 cm. to the left of the midcla icular line Tachycardia was present with regular rhythm. No murmurs were noted. The remainder of the physical examination was normal.

During the course of the examination, the patient began to complain of severe substernal chest pain and diaphoresis. Systolic blood pressure fell to 90 mm. Hg The electrocardiogram (ECG) was interpreted as consistent with an acute anteroseptal myocardial infarction.

Laboratory data. The urine was acid with specific gravity 1.021 There was one-plus albuminuria. Microscopic examination of the urine sediment was negative Hemoglobin was 10.5 grams, white blood cou t (WBC) was 9,100 per cubic millimeter with 85 per cent neutrophils, 8 per cent lymphocytes, and 7 per cent monocytes. Blood urea nitrogen (BUN) was 11 mg per cent, uric acid 9 1 mg per cent, serum alkaline phosphatase 3.0 Bessey Lowry units serum glutamic oxalacetic transaminase (SGOT) 36 lactic dehydrogenase (LDH) 106 Skin tests for histoplasmosis and the intermediate strength purified protein derivative (PPD) showed 1 cm. areas of induration at 72 hours Sputum studies were negative for acid fast bacilli and for tumor cells. Complement-fixation tests for blastomycosis coccidioidomycosis, and histoplasmosis were nonreactive.

A chest x-ray showed right pleural effusion and considerable pleural reaction.

Following the acute episode of chest pain, the patient continued to complain of less severe chest pain intermittently but gradually improved, although transient episodes of cardiac arrhythmia and weakness occurred on occasion. H was given digitalis following an episode of supraventricular tachycardia and required pressor agents to maintai his blood pressure for tw days.

By late June his condition was considered satisfactory for investigation of the pleural effusion. Right thoracentesis yielded 200 of yellow slightly turbid fluid pleural biopsy was attempted. Both procedures ere repeated fi days later The cell

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cou t on the initial fluid was 360 with a preponderance of lymphocytes. Protein was 5 Gm. per cent. Cytology nd cell-block preparations were negative for tumor Culture was negative. The pleural biopsy specimens were reported as striated muscle.

Postthoracentesis chest films revealed two nodular densities in the right midlung field

F llowing these procedures, the patient developed progressive mental confusion which was more pronounced at ight Electroencephalogram (EEG) re ealed generalized slowing of activity Brai sca following administration of radioactive mercury 203 revealed no focal lesions. Serum calcium was 13.5 and phosphoru 2.6 mg. per 100 ml. Repeated examinations yielded th same val es.

The patient was started on teroids but despite therapy exhibited progressive deterioration clinically and on J ly 6 1966, was noted to ha e cyanosis of the face nd neck without peripheral cyanosis. He developed increasing respiratory distress nd the venous pressure measured in the right tecubital vein was elevated to 550 mm H_2O A superior vena cavagram revealed obstruction t the level of the pericardial reflection Because the bstruction was strongly suspected to be neoplastic, 20 mg of itrogen mustard was admi istered travenously but th patient exhibited progressive respiratory distress despite therapy and died i respiratory failure on July 8 1966.

Clinical discussion

DR JOHN HANDY* The major diagnostic problem confronting the clinician late in the course of this patient s illness was to clarify the cause of the obstruction to blood flow through the right side of the heart. A correct answer to this question would quite likely lead to the correct diagnosis.

In 1963 oral cancer was surgically removed without apparent local spread. This important fact dominates the remainder of the history for one must be highly suspic ious of all subsequent symptomatology in such a patient as being due to recurrence of cancer As Dr W M Yater remarked[1]

If in a person who is known to harbor a malignant neoplasm cardiac symptoms develop which cannot be otherwise ex plained it is reasonable to assume that metastatic invasion of the heart has oc curred The patient returned $2\frac{1}{2}$ years later with chest pain which was somewhat suggestive of coronary insufficiency He was dyspneic on exertion without orthopnea paroxysmal nocturnal dyspnea or edema The dyspnea and pain were perhaps the first clues pointing toward obstruction to venous inflow to the right side of the heart The pulse was 130 The patient was plethoric, which is unusual when associated with a hemoglobin of only 10 5 grams and suggests obstruction of venous return to the heart Signs of right sided pleural effusion and cardiomegaly were present. Anemia elevated serum uric acid alkaline phosphatase at the upper range of normal and normal SGOT with elevated LDH all suggest the presence of neoplasm as the cause of the right heart obstruction

During the examination chest pain and hypotension appeared which strongly sug gested coronary occlusion or a pulmonary embolism. An ECG was compatible with an acute anterior myocardial infarction Arrhythmias appeared which were treated with digitalis. Pressor agents were administered for two days. Thoracentesis revealed sterile nonbloody fluid with an elevated protein and many lymphocytes, but no malignant cells. These findings are compatible with inflammation or cancer but not cardiac failure. Two attempted biopsies

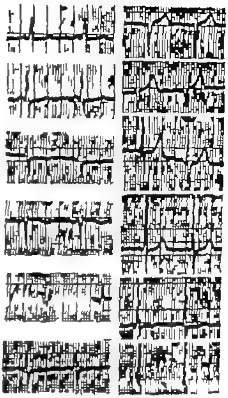

Fig 1 ECG considered within normal limits.

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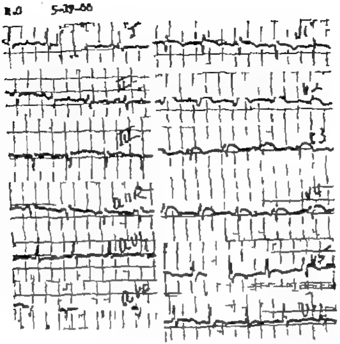

Fig. 2 ECG demonstrated left axis deviation, S-T elevation, and T-wave inversion. These findings are compatible with acute myocardial injury.

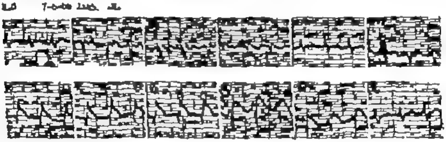

Fig. 3 ECG showed supraventricular tachycardia, elevated S-T segments, inverted T waves with loss of R waves. These findings when compared with previous tracings suggested myocardial or pericardial disease.

of pleura yielded only muscle fragments. Like many tests, negative results from a needle biopsy are meaningless. They certainly do not indicate that the disease in question is not present. Mental confusion appeared and an EEG and brain scan were normal, as is often the case in absence of focal signs on neurologic examination. In view of the mental confusion, elevated calcium and low phosphorus appear significant and perhaps causal. The patient's physicians evidently decided that hypercalcemia was secondary to neoplasm. Steroids were administered in an attempt to lower the calcium, and nitrogen mustard was given for its effect on the neoplasm. Despite these measures, dyspnea increased and was associated with elevation of the superior vena cava pressure. The patient continued to deteriorate and died with cyanosis of the face and neck.

In 1963 his ECG was normal (Fig. 1). The subsequent ECG (Fig.) obtained two days following the hypotensive ep[illegible]

Fig. 4. Relative to the 1963 film, the 1966 admission x-ray reveals an enlarged cardiac shadow and right pleural effusion without pulmonary edema.

showed left axis deviation, S-T elevation, and T wave inversion. These changes were interpreted as suggesting fresh myocardial infarction. However, the usual evolutionary changes as seen in myocardial infarction failed to occur during the ensuing two months, and, in fact, the S-T elevation became more pronounced. Supraventricular arrhythmias subsequently appeared. An ECG obtained two days prior to death demonstrated marked elevation of the S-T segments over the right precordium with low voltage (Fig. 3). These unusual findings were considered suggestive of pericardial or myocardial disease, or perhaps pulmonary embolism. May we see the x-rays?

DR. M. PINSON NEAL, JR.* The chest film taken in 1966 shows that the cardiac shadow is enlarged relative to the 1963 study (Fig. 4). In addition to the evidence of cardiomegaly, right pleural effusion is present. There is no evidence of heart failure in terms of pulmonary edema. One observes minimal fullness that in the older person may represent vascular markings when associated with kyphosis. Films taken two weeks after the removal of chest fluid demonstrate that the heart size is unchanged and small densities are present which are uniform, soft, and noncalcified. The planogram (Fig. 5) further defines these lesions. Knowing the patient's history and seeing the pleural effusion, we believe that these lesions represent metastases.

The superior vena cava study (Fig. 6) reveals contrast material passing via the right arm and entering the superior vena cava with a very straight, rigid, and fixed appearance. A network of small abnormal vessels is present. One sees reflux and impingement. As we observe contrast material passing through the cava at the pericardial reflection, a space-occupying, somewhat diamond-shaped density having the appearance of a thrombus is visualized. As the contrast medium enters the right side of the heart, it has a tapered appearance. This latter abnormality is the type of finding one sees with a neoplastic obstruction rather than a filling defect characteristic of thrombus formation. It would appear that there is tumor involvement in this area with fixation in the region of the superior mediastinum. Extrinsic pressure upon the vein may be present with neoplastic encroachment restricting and preventing any significant degree of contrast material from entering the right side of the heart. Adjacent thrombus may also be present.

DR. HANDY: Do you see any signs of pericardial disease on the x-rays?

DR. NEAL: There doesn't appear to be, but if we judge pericardial disease only from plain films, pericardial effusion may be missed. Since there is disease at the pericardial reflection, I am sure the process has involved the pericardium.

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Fig. 3 The planogram taken after thoracentesis reveals small, noncalcified densities.

Fig. 4 In this superior vena cavagram the cava has a rigid, fixed appearance. A diamond-shaped density at the level of the pericardial reflection suggests the presence of a thrombus. Compression and tapering of the jet suggests extrinsic pressure upon the vein and right heart.

DR. HANDY You see no pericardial thickening though?

DR. NEAL No sir

DR. HANDY How about signs of hyperparathyroidism on these x-rays?

DR. NEAL We reviewed many films with this in mind because of the calcium and phosphorus abnormalities, but saw no evidence of bone lesions suggestive of hyperparathyroidism.

DR. HANDY Do you have any reason from the x rays to explain the enlargement of the heart?

DR. NEAL No. As I pointed out during the earlier films, the cardiac silhouette was enlarged without evidence of failure It definitely had enlarged in the last two years.

DR. HANDY Do you see evidence of ventricular aneurysm in the lateral view of the chest

DR. NEAL No sir

DR. HUDSON Dr Neal you seem convinced that the man has a tumor Do you see anything in the lungs that would suggest primary tumor? Is there anything in the bones that might suggest metastatic disease possibly explaining the changes in the calcium and phosphorus levels?

DR. NEAL The bones that we have on the films of the chest and of abdomen as interpreted from an intravenous pyelogram (IVP) failed to show any significant bony metastases. You will recall the discrete chest lesions that we saw after the fluid was removed. We apparently have extrinsic disease throughout the mediastinum It would be unlikely to have a minute primary in the lung causing so much mediastinal disease.

DR. HANDY Do you think his pleural effusion is due to the lesions seen in the lungs?

DR. NEAL I think that this is a reasonable assumption since there are no other roentgen signs of cardiac failure.

DR. HANDY The radiologic findings combined with the clinical story suggest to me an obstruction of the superior vena cava. The low voltage of the ECG suggests disease of the pericardium or myocardium. Deep Q waves with S-T segment elevation and inverted T waves that do not change are characteristic of pericardial and/or myocardial metastasis although many other ECG abnormalities have been reported.

Supraventricular tachycardias are quite common in metastatic heart disease and this patient had such arrhythmias. The x-rays demonstrated a filling defect of the superior vena cava and cardiomegaly. The cardiomegaly could be due to pericardial or myocardial metastasis. The cardiomegaly and ECG are not solely suggestive of the superior vena cava syndrome. Therefore I would say that metastatic disease involving the right side of the heart, pericardium, and superior vena cava is quite likely. The pleural effusion is disturbing and perhaps represents pleural metastasis.

What about nonneoplastic disease in this patient's differential diagnosis? Many patients who die with oral cancer are found at autopsy to have tuberculosis. The tuberculin skin test was positive and the ECG was entirely compatible with constrictive pericarditis. However, we still have to explain apparent cardiomegaly; the x-rays show no evidence of constrictive pericarditis. Other granulomatous disease would seem unlikely for the same reasons. Over 80 per cent of patients with superior vena cava syndrome have cancer; the others have dissecting aneurysm or granulomatous adenopathy. No aneurysm was seen radiologically. There is no other evidence of granulomatous disease.

If this is metastatic disease, where is the primary? The appearance of metastatic tumors after the primary oral cancer was considered to have been completely eradicated is not common. Formerly these reappearances from head and neck cancer were thought to occur only above the clavicle. Such is not the case. There are in fact frequent metastases beneath the clavicle with spread via the lymphatics down the mediastinum.

DR. JOHN H. MOON*: Would you consider a primary cardiac tumor?

DR. HANDY: This is an attractive diagnosis in this patient and there is little clinically incompatible with it. It most likely would be a sarcoma originating in the heart or pericardium and thence invading the myocardium with further extension into the superior vena cava with sparing of the inferior vena cava.

What about a myocardial infarction? I do not think it would explain all the findings. The failure of resolution of the ECG changes and the high venous pressure in the upper extremities without liver enlargement or edema are points against myocardial infarction with pulmonary edema. The ECG is also compatible with pulmonary infarction but x-rays are not suggestive solely of pulmonary infarction.

DR. HUDSON: Would you elaborate on the calcium and phosphorus abnormalities?

DR. HANDY: We have the unusual combination of an elevated serum calcium and a low serum phosphorus. I believe that only one situation truly produces an elevated serum calcium and low phosphorus, and that is excessive parathyroid hormone. There are of course reports of vitamin D intoxication and sarcoid associated with hypercalcemia and hypophosphatemia but these are very rare and isolated. I guess Dr. Neal tells us the bone films do not look like primary hyperparathyroidism. I am going to say that he doesn't have primary hyperparathyroidism. I do not believe the patient has cancer of the parathyroid with metastasis to the mediastinum since parathyroid cancer usually spreads locally and should have produced readily apparent metastatic disease in the neck nodes. If excessive parathyroid secretion is not arising from the parathyroid gland, where is its origin? The tumor itself is most likely secreting the hormone. This alteration is found in the syndrome of pseudohyperparathyroidism with primary tumors and/or metastases producing parathyroidlike peptides and this may occur in the absence of demonstrable bony metastasis.

Dr. Lafferty recently reviewed 50 patients with this syndrome: 30 per cent had hypernephroma, the other 30 per cent had lung cancer, and the remaining 40 per cent had a wide variety of tumors.

There are features that help separate primary hyperparathyroidism from pseudohyperparathyroidism. A history of kidney ... renal ... sm is ... nhill ... of a primary tumor while primary hyperparathyroidism is an indolent disease often present for years before removal of the adenoma. The absence of stones and the

*Associate Professor, Department of Medicine

relatively brief course of this patient suggests cancer. In pseudohyperparathyroidism the physical examination often reveals evidence of the underlying cancer while in primary hyperparathyroidism the physical examination is usually normal. Dr. Lafferty pointed out the serum chlorides are often greater than 102 mEq. per liter in primary hyperparathyroidism and less than 102 mEq. per liter in patients with hypercalcemia of other causes. Our patient's serum chloride was 92 and 97, again leading us to suspect pseudohyperparathyroidism. The borderline alkaline phosphatase in this patient is not of much help. The serum calcium in pseudohyperparathyroidism is often 14 mg. per cent or higher while most patients with primary hyperparathyroidism have calcium levels in the 11 to 13 range. This patient's level of 13.5 mg. per cent is not helpful in differentiating the two diseases. Other tests used to diagnose primary hyperparathyroidism such as tubular absorption of phosphate and calcium infusion are usually not helpful in a patient such as this one. I conclude then that our patient had metastatic cancer associated with parathormone-like activity. As a second choice I choose primary sarcoma of the heart with myocardial, pericardial, pleural, and superior vena cava metastasis.

DR. FAIRFIELD GOODALE:* There were two cytology examinations of the pleural fluid reported as negative for tumor cells. Supposing there is carcinoma, this is mildly disturbing. Dr. Kay, how often in the presence of metastatic carcinoma would you get two negative cytologies?

DR. SAUL KAY:** One would have to have the pleura involved with the tumor shedding into the pleural space to have tumor cells there. Sometimes the metastasis is only in the chest wall and there can then be an effusion without tumor cells in it.

DR. GOODALE: Give us a number. How often would you find two negative cytology studies in the presence of metastatic cancer in the chest wall and lung causing effusion?

DR. KAY: The majority would have exfoliated cells at some time. I cannot tell you what percentage. I think it depends on the number of fluid samples taken.

DR. EDWARD RAY:* With three separate specimens examined per patient, at least ¾ of the patients with metastatic chest cancer yield tumor cells.

DR. RUSSELL RANDALL:** When the patient first came in, the house staff appreciated his neck vein distention and even though he was having what we thought was an infarct, we suspected superior vena cava obstruction of some type. When he had his full blown obstruction with cyanosis, he looked as if he might have the carcinoid syndrome with tremendous ruddy cyanosis of the upper extremities and particularly the face. He also had some telangiectasis across his chest wall as may be seen in superior obstruction.

DR. MOON: What were the senior students' opinions today?

MR. THOMAS G. DAY, JR.:*** Most of the seniors agreed that the patient had the superior vena cava syndrome. A total of 39 thought primary carcinoma of the heart was the cause. Metastatic carcinoma of the heart secondary to carcinoma of the oral cavity was indicated by 41. Six suggested Hodgkin's disease.

WARD DIAGNOSES: Myocardial infarction, metastatic carcinoma with parathormone activity.

DR. JOHN HANDY'S DIAGNOSIS: Metastatic squamous cancer (from floor of mouth) to myocardium, pericardium, and pleura, superior vena cava syndrome, parathormone-like activity, possible primary sarcoma of the heart.

Pathological discussion

DR. PAGE HUDSON: The lesion in 1963 was a cm. invasive squamous cell neoplasm on the floor of the mouth immediately adjacent to the undersurface of the tongue. The floor of the mouth, the adjacent edge of the tongue, part of the mandible, and the appropriate soft tissue of the neck were resected. No metastatic tumor was present in the 60-plus lymph nodes. This is not an uncommon site and this lesion, like other oral squamous cancers, is rare in nonsmokers.

At the autopsy table marked neck vein distention was still apparent though the

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*Professor and Chairman, Division of Pulmonary Diseases.
**Professor and Chairman, Division of Renal Medicine.
***Senior student.

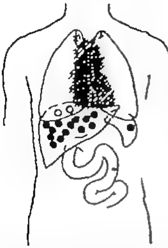

Fig. 7. Metastatic tumor coated the epicardial, pericardial, and adjacent pleural surfaces. The neoplasm was massed among the great vessels. Metastases were also noted in the lung, liver, spleen, and jejunum as noted in the diagram.

Fig. 8. Metastatic tumor masses (arrows) were present within the myocardium as shown here in part. (Hematoxylin and eosin stain; original magnification ×2.)

florid color had blanched. When the chest had been opened, the prosector, Dr. Donald McNeil, observed that massive tumor replaced or surrounded many of the mediastinal structures and extended into the right pleura (Fig. 7). The pericardial sac was heavily involved. The superior vena cava was compressed by tumor and was nearly occluded by an organizing thrombus that had formed at the point of constriction. Tumor replaced much of the right ventricle as Dr. Handy suspected. The left ventricular muscle had tumor continuous with the pericardium but also separate metastases (Fig. 8). The tumor had a microscopic appearance identical to that of the original lesion (Fig. 9). Dr. Handy, there is complete agreement between the cardiopericardial morphology and the interpretation rendered by you and your cardiac consults.

About 10 per cent of the liver was replaced by neoplasm. Tumor was present in the spleen and in the wall of the jejunum. The cerebellum was the seat of the degenerative change seen in many malnutrition syndromes and in some cancer cases that are without the usual evidence of malnutrition. This, morphologically, is manifested primarily by loss of Purkinje cells and by cerebellar granular layer degeneration.

A rather recent pulmonary embolus was present in the right pulmonary artery. No gross or histological abnormalities of the parathyroid glands or of the kidneys were present.

DR. HANDY: Were there bone metastases to account for the calcium and phosphorus changes?

DR. HUDSON: There was a single small rib lesion which would certainly not account for those abnormalities.

His original neoplasm was in an exposed area where it could easily have been seen, as is the case with most oral cancers. The floor of the mouth is the location of about 15 per cent of oral malignancies. The five-year survival rate is only about 30 per cent.

We are in the ascendency of a great awareness of endocrine activity of malignant neoplasms, particularly those arising from nonendocrine tissues. Dr. Handy suspects this tumor had parathyroid hormone activity to cause the calcium-phosphorus changes. We shall see. This concept of cancer endocrine activity is, to me, one of the most exciting in the field of biology. That almost any cell type of lung,

Fig. 9. The squamous cell epithelioma had the same histologic appearance in the original lesion and numerous metastases. The malarranged malignant cells are interrupted by frequent squamous plugs or pearls.

kidney, liver, colon, skin cancer may produce ACTH, parathormone, estrogenlike activity, or erythropoietin and other complex substances, presents new horizons and new challenges. The tumor-induced endocrinopathies such as hyperparathyroidism, Cushing's disease, pseudopolycythemia, and so forth may mask the malignancy. Therefore, the presence of endocrine abnormalities should make the physician suspect an underlying neoplasm. Admittedly, these changes are, more often than not, biochemical abnormalities without clinical signs or symptoms. Some of the more common syndromes are those of Cushing-like effect with lung tumors, hypercalcemia, or polycythemia with renal lesions, hypoglycemia with large neoplasms, particularly sarcomas.

I believe that other unexplained phenomena associated with malignancies will soon be shown to be caused by specific products of the neoplasm. These will include the leukemoid reaction, fever, emaciation, and cerebellar degeneration.

DR. MOON: How do you account for the original synthesis of a complicated molecule by the primitive cells of a poorly differentiated malignancy?

DR. HUDSON: The answer is not yet known, but you might consider that all cells have certain common functions and are presumably endowed with DNA containing the same information. The multiple alterations involved in malignant degeneration may include unmasking or deinhibiting some of the latent abilities that all cells have, more specifically, synthesis of proteins and peptides.

To summarize our case today, this was a patient who had a squamous cell epithelioma of the floor of the mouth. He was, by the way, a heavy smoker. Radical surgery revealed no metastases. The latter did appear 2½ years later, involving the mediastinum and its structures primarily. Clinically, his metastases simulated primary heart disease. He had superior vena cava obstruction, cerebellar degeneration, calcium and phosphorus aberrations, and eventually succumbed to a pulmonary embolism. Dr. Randall has something further to tell us about the tumor from today's patient.

DR. RANDALL: Part of the tumor removed at autopsy was frozen and hand-carried to the laboratory of Dr. Armen H. Tashjian, Jr., at the Harvard Dental School Biological Research Laboratories. He has developed an antibody against parathyroid hormones and uses a competitive inhibition for assay of the tumor. He told me by telephone this morning that there is an abnormally high level of parathyroid hormone in that squamous metastatic neoplasm.

He is attempting to grow tumors with this type of apparent activity in cell culture to study the nature of hormone production.

DR. HUDSON: Dr. Grant Liddle[4] has shown ACTH production by tumor growing in tissue culture taken from a patient who did have Cushing's syndrome associated with carcinoma of the lung.

DR. HANDY: At our McGuire VA Hospital within the last three months we have had four such patients. Three of them are now in our metabolic ward and the fourth one has since died, so in our experience the phenomenon is not very rare. We have good

results by treating the hypercalcemia with massive doses of steroids. One man was given 2 Gm of intravenous hydrocortisone over a 12 hour period and his calcium fell from 17 to 13 within a 12 hour period. Intravenous phosphates have also been useful.

DR JULIO H GARCIA.* The type of cerebellar lesion this patient had initially was long held to be peculiar to alcoholics. The ataxia that is so well associated with chronic alcoholism is attributed to this particular lesion in the vermis however it is more commonly seen now in people with neoplasms[5] and occasionally general malnutrition states. I think this ties in very well with the possibility Dr Hudson was mentioning that perhaps it is due to some substance produced by cancer an anti vitamin and thus causes a malnutrition lesion.

DR KAY Was there pleural involvement that might have produced exfoliated cells in the pleural fluid

DR. HUDSON There was some tumor on the pleura. A review of the antemortem pleural fluid PAP's, and cell blocks did not reveal tumor cells.

DR KAY What about the two lumps seen in the right lower lobe in the later x rays

DR HUDSON There were pulmonary metastases

DR GOODALL I would like to ask Dr Handy how he ruled out primary carcinoma of the lung

DR HANDY I did not rule it out I could not He had had one cancer and I considered that a change in his temporarily stable state was more likely to be due to metastases than to a new tumor This admittedly is dangerous As you know a person with one squamous cell lesion of the mouth larynx or lung is much more likely to have another lesion in one of those sites than a person who has never had one More likely there is the same etiological factor smoking with all three areas.

Final diagnosis

Squamous cell epithelioma of the heart pericardium mediastinum and superior vena cava also lung pleura liver rib spleen and jejunum following squamous cell epithelioma of the floor of the mouth parathormone like activity of the metastases thrombosis with near occlusion of superior vena cava pulmonary embolus subacute cerebellar degeneration

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REFERENCES

1 Yater W M Tumors of the heart and pericardium Arch Int Med 48:627 1931
2 Fischel, H C J and Pinson D L Superior vena caval canal obstruction Dis. Chest 49 155 1966.
3 Laffert F W Pseudohyperparathyroidism, Medicine 18:247 1966
4 Liddle, C W Givens, J R Nicholson, W E and Island, D P The ectopic ACTH syndrome Canad Res. 25 1057 1965
5 Brain, I and Wilkinson M Subacute cerebellar degeneration associated with neoplasms Brain 88:465 1965

Recent advances in the differential diagnosis of A-V junctional arrhythmias

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Richard Langendorf
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Perhaps in no other aspect of clinical electrocardiography has such spectacular progress been made in recent years as in the understanding and differential diagnosis of the mechanisms of arrhythmias involving A-V junctional tissues. Much of the credit for these advances goes to electrophysiologists, who have placed electrodes directly on the conduction system[illegible] or pierced its cells with microelectrodes.[illegible] But some information was also provided by experiments on the human heart which became feasible with the introduction of artificial pacing for treatment of the Stokes-Adams syndrome.[illegible] Last but not least, valuable contributions have resulted from the awakened interest of embryologists in the development of[illegible] and of pathologists in the structure[illegible] and ultrastructure[illegible] of the conduction system under normal and pathological conditions.

In general, these experimental observations have fortified most of the concepts which the clinical electrocardiographer had developed[illegible] on the basis of deduction and speculation. On the other hand, the new information has also caused the clinical electrocardiographer to revise some well-entrenched ideas concerning the two functions of the specialized system, impulse conduction and impulse generation.[illegible] One of the concepts that has undergone revision is the designation of certain supraventricular rhythms as "upper, middle, and lower nodal" rhythms.[illegible] It is now quite clear that such a classification is misleading for several different reasons: (1) automaticity of specific cells of the central area of nodal tissues (the N-region) has, to our knowledge, not been demonstrated,[illegible] probably due to its low threshold of excitability;[illegible] (2) relationships of retrograd P waves to QRS are not only dependent on the proximity of the ectopic pacemaker to atria or ventricles but also on the relative speed of conduction in either direction;[illegible] and (3) experimentally proved retrograde atrial activation may produce, against the rule, upright P waves in Leads II, III, and aV_F.[illegible] Consequently, we have abandoned the use of the term nodal rhythms and adopted instead the more comprehensive designation A-V junctional rhythms (or

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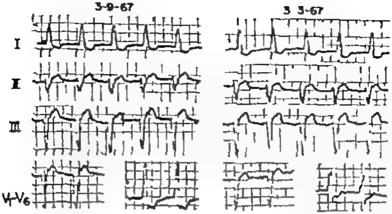

Fig. 1. ECG's of a 66-year-old woman with arteriosclerotic heart disease taken while the patient was receiving digitalis. The records are mounted in reverse order for purposes of presentation. *3-9-67*: accelerated ectopic low atrial or A-V junctional rhythm with first-degree A-V block (P-R 0.58 sec.) and LBBB. Without comparison with the record of *3-3*, a ventricular or "lower nodal" rhythm with retrograde P waves following each QRS might have been diagnosed.

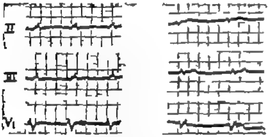

Fig. 2. ECG of a 53-year-old woman with myocardiopathy taken after conversion of atrial fibrillation by quinidine. The two records were obtained 11 days apart while the patient was taking digitalis. In both there are retrograde P waves (upright and best seen in V1), in the first record preceding and in the second following small QRS complexes. Development of a first-degree retrograde block, changing the QRS-P relationship, is more likely than a shift of a faster "upper" to a slower "lower nodal" rhythm.

premature beats or tachycardias).[40] This designation has been accepted by others[41,124] and is applied throughout this presentation. One consequence of this change has been the elimination both of the semantic difficulties and of the attempts at differential diagnosis of ectopic beats and rhythms arising in the region of the coronary sinus.[22,118] These disturbances in rhythm are now included in the designation of "low atrial rhythm" or alternatively of "A-V junctional rhythm" (Figs. 1, 2, and 32).

Table I. Mechanisms to be considered in the differential diagnosis of A-V junctional arrhythmias

1. A-V dissociation with, and without, A-V block
2. A-V junctional parasystole
3. Two or more regions of block, and unidirectional block, *in the A-V junction*
4. Reciprocal beating of ventricles and/or atria
5. Bilateral BBB as a cause of A-V block
6. Variants of Type I A-V block
7. Concealed conduction in the A-V junction
8. Alternation of A-V conduction
9. Multiple A-V pathways

Conceptual as well as semantic problems have accompanied the growth of knowledge about the physiology and pathology of the A-V junction. Nine such problems which are frequently encountered in the analysis of clinical electrocardiograms (ECG's) are listed in Table I. Representative examples will be illustrated and briefly described with reference to recent publications. Since it is usually difficult or impossible to separate strictly disorders of impulse formation from those of impulse conduction because of their interdependence,[22] the outstanding feature of the arrhythmia will be used as the basis of the classification.

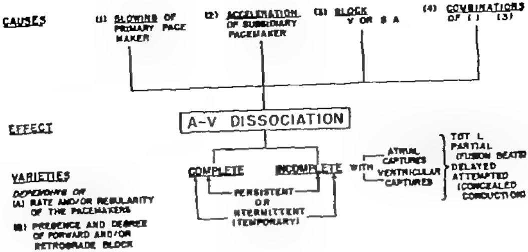

Fig 3 Causes and varieties of A-V dissociation.

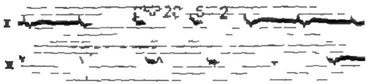

Fig 4 ECG of 61-year-old man with an old anterior wall infarct, taken while the patient was receiving digitalis. Transitions of A-V junctional rhythm with retrograde conduction into A-V dissociation, and vice versa, in marked sinus bradycardia and arrhythmia. P waves in the two middle beats of Lead III represent atrial fusion beats (partial atrial capture).

Discussion

A-V dissociation with and without A-V block and its varieties Our approach to the interpretation of the many facets of A-V dissociation[11,25] is based on the fact that A-V dissociation is never a primary disturbance of rhythm but merely a secondary consequence of a basic disturbance of impulse formation and/or conduction.[21] In the upper part of Fig 3 are enumerated the four causes slowing of the primary pacemaker acceleration of a subsidiary pacemaker A-V or S-A block, and various combinations of these mechanisms. In the lower part are listed the varieties of A-V dissociation that result from variations in the rate of pacemaker discharge and in the degree of block if a block is present. The most important of these varieties are complete or incomplete A-V dissociation.

Complete A-V dissociation[11] means entirely independent action of the atria and ventricles none of the antegrade atrial impulses succeed in capturing the ventricles nor does any retrograde ectopic impulse traverse and capture the atria. In the incomplete variety on the other hand capture of ventricles or atria may be total or partial the latter manifested by atrial or ventricular fusion beats. Complete or incomplete A-V dissociation may persist for a long while or may be transient, coming and going as the relative rates of the two operating pacemakers vary For instance Fig 4 shows how readily A-V dissociation, induced during a sinus bradycardia by repetitive junctional escapes, yields to A-V junctional rhythm with retrograde activation of the atria when the sinus rate slows. Fig 5 on the other hand shows two different examples in which intermittence of A-V dissociation was

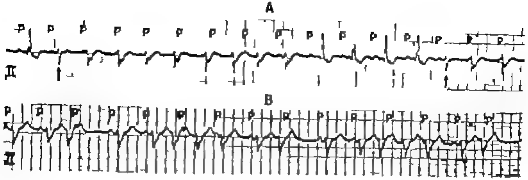

Fig. 5. Atherosclerotic heart disease shown in ECG of 77-year-old man (*A*) and 67-year-old man (*B*). In both records A-V dissociation is present during irregular runs of a repetitive paroxysmal ectopic tachycardia. The arrows in *A* point to ventricular fusion beats (partial ventricular capture). In *B* conducted sinus beats and ectopic beats have the same contour. The fallacy of diagnosing a ventricular origin of an ectopic rhythm on the basis of temporary or permanent independence of atrial and ventricular action is clearly revealed (see text).

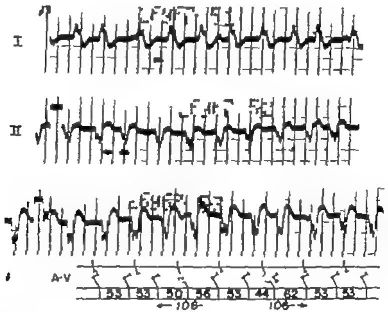

Fig. 6. ECG of a 44-year-old man with hypertensive heart disease, taken while the patient was receiving digitalis. Incomplete A-V dissociation caused by parasystolic A-V junctional tachycardia (rate 112) with retrograde block. *Junctional origin of the parasystolic pacemaker is revealed by the identical contour of ectopic and conducted beats.* Its regular discharge is indicated in the diagram by the dots at the A-V level, its protection from conducted sinus impulses by the stippled half circles bypassing these dots.

caused by the intermittent and irregular activity of an accelerated *ectopic* pacemaker with widened *QRS* complexes. *Furthermore*, *comparison* of the two records also demonstrates that, contrary to popular notions,[illegible] it is not possible to diagnose a ventricular origin of an ectopic tachycardia merely because atrial and ventricular activity are independent.[illegible]

In record A the diagnosis of a ventricular tachycardia is suggested by *the occurrence of ventricular fusion* beats (↑). In record B the identical contour of both the conducted and the ectopic beats indicates that the A-V junction is the site of origin of the intermittent tachycardia (Fig. 6).

As a rule, ventricular *captures* in *incomplete* A-V dissociation discharge the

ectopic pacemaker and may transiently depress it[21] (see Fig 15) unless it is protected and acts as a parasystolic pacemaker. This protection is more commonly seen with ectopic foci of the ventricles[22] than with A-V junctional centers. One such case is illustrated and analyzed with the help of a diagram in Fig 6. Apart from the parasystole, it illustrates again the problem of distinguishing between a supraventricular and a ventricular tachycardia when abnormally wide and irregularly spaced QRS complexes co-exist with a predominantly independent action of atria and ventricles. The distinction between ventricular and A-V junctional parasystolic rhythms has practical importance since the latter may occur in normal hearts.[23,24] In the case of left bundle branch block (LBBB) illustrated in Fig 6 the junctional parasystole was induced by the development of a nonparoxysmal A-V junctional tachycardia with complete retrograde block, as a consequence of digitalis medication.

A nonparoxysmal variety of A-V junctional tachycardia[25] is a common cause of complete or incomplete A-V dissociation. It may occur as a manifestation of a transient pathological state of the A-V junctional tissues with or without simultaneous depression of A-V conduction. Fig 7 shows records taken on successive days in a child with acute rheumatic fever. Myocardial involvement by the rheumatic process is revealed by the transient acceleration in the rate of A-V junctional escape. Although the same degree of sinus arrhythmia is present on both days, A-V dissociation is found only on the first. Such a fleeting A-V junctional tachycardia, causing transient A-V dissociation is also commonly seen in cases of recent posterior wall infarction.[26]

If the sinus rate varies slightly and if the accelerated A-V junctional discharge rate happens to be within range of the sinus cycles, a so-called "isorhythmic A-V dissociation" may result (Fig 8). That this is a chance phenomenon[27] rather than the clinical equivalent of the specific mechanism of "accrochage"[28,29] is revealed by (1) the ready break of the apparent link of the two rhythms when the rate of the two centers changes spontaneously

Fig 7 ECG of a 12 year-old girl with acute rheumatic fever. The records were taken two days apart. Transient acceleration of the A-V junctional escape rate causes intermittent A-V dissociation in the upper record. Note normal P-R intervals indicating absence of A-V block.

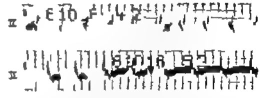

Fig 8 ECG of a 56-year-old man with chronic endobronchial disease. Digitalis has produced nonparoxysmal A-V junctional tachycardia with isorhythmic A-V dissociation in the upper record and retrograde activation of the atria 4 days later after slowing of the sinus rate (see Fig 4).

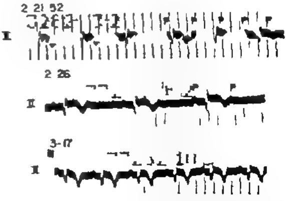

Fig 9 ECG of a 72 year-old man with recent posterior wall infarction. Transient complete A-V dissociation on 2-21 is caused by the combination of A-V block with temporary acceleration of A-V junctional impulse formation. The latter is suggested by the failure of A-V junctional escapes to occur on 2-26 during 2:1 A-V block. Conceivably, however, escapes could be prevented by concealed A-V conduction of every other sinus impulse (see Figs. 24 and 34).

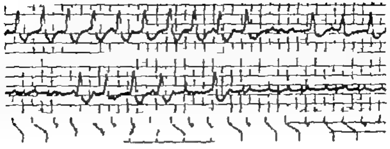

Fig. 10. ECG of a 32-year-old man with hypertensive heart disease. The presence of a second degree A-V block (in a sinus tachycardia) is revealed only during intermittence of an ectopic tachycardia causing temporary A-V dissociation (see diagram). Ventricular origin of the accelerated ectopic rhythm is suggested by the occurrence of a ventricular fusion beat (*F*).

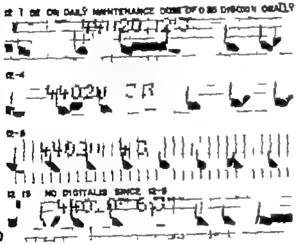

Fig. 11. ECG of a 60-year-old woman with atherosclerotic heart disease. Gradual acceleration and deceleration of the A-V junctional escape rate (*E*) in atrial fibrillation causing complete A-V dissociation on *12-4* and *12-5*.

or after exercise or pressure on the carotid sinus, (2) the lack of any synchronization of atrial and ventricular action in long-standing cases of complete A-V block, and (3) failure of atrial and ventricular synchronization to develop during artificial pacing of the ventricles.

The absence of any A-V block in A-V dissociation caused by nonparoxysmal A-V junctional tachycardia is evidenced by the normal P-R interval of conducted beats (Fig. 7). However, as demonstrated in Fig. 9, a temporary nonparoxysmal A-V junctional tachycardia may co-exist with a transient first- or second-degree A-V block. This combination and not complete A-V block is responsible for the complete A-V dissociation in the tracing taken on February 21. Recognition of this combination of functional disorders may spare the patient with a recent infarction of the posterior wall the use of artificial cardiac pacing[11,27,28] since the disorder is usually transient in such patients.[1,33,36] This benign prospect contrasts with that of A-V block in anteroseptal infarction in which block is usually caused by anatomical involvement of the two bundle branches[1,66] (see below). The possibility of overlooking the co-existence of an A-V block with acceleration of an ectopic focus is illustrated in Fig. 10. In this case of a ventricular tachycardia, evidenced by the fusion beat, a 3:2 A-V block is seen only during intermission of the ectopic discharge.

The combination of a mild degree of A-V block with acceleration of the rate of A-V junctional impulses is the hallmark of digitalis effects in atrial fibrillation. In the ECG of Fig. 11 obtained on December 1 from a patient who had received full doses of digitalis, an A-V junctional pacemaker, E, escaped at a slow rate of 48 per minute. As digitalization was continued, the regular discharge of this pacemaker progressively accelerated to produce complete dissociation of the ventricles from the fibrillating atria; the junctional pacemaker slowed after digitalis was discontinued. Sometimes, however, while A-V dissociation continues, the ventricular rate may slow rather than accelerate during

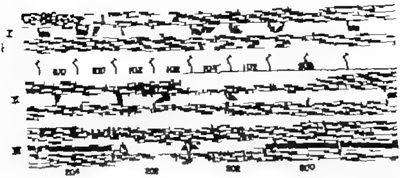

Fig *12* ECG of a 74-year-old man with atherosclerotic heart disease, taken while the patient was receiving digitalis. Atrial fibrillation with complete A V dissociation A slow A V junctional rhythm is simulated by 2 1 exit block of junctional impulses at the end of Lead I (see diagram) and throughout Leads II and III

Fig *13* ECG of 59-year-old man with atherosclerotic heart disease, taken while the patient was receiving digitalis. Second-degree block (Type I) in the lower A-V junction causing irregular ventricular rate in atrial fibrillation with complete A V dissociation. Intervals between beats terminating pauses in Lead I are precise multiples (4 times and 3 times, respectively) of the regular cycle of nonparoxysmal A-V junctional tachycardia in Lead III *The irregular spacing in Lead I reveals the structure of* Wenckebach periods with 4 3 and 3 2 conduction ratios, the latter resulting in ventricular bigeminy

the administration of digitalis, as illustrated in Fig 12. In this instance the drug produced two regions of block in the A-V junction an upper one completely separating the fibrillating atria from the junctional pacemaker and a lower one responding to the impulses from the junctional center at a 2 1 ratio.[10] It follows, therefore that any digitalis-induced complete A V dissociation in which the A V junctional rate is moderate or slow may represent a junctional tachycardia with two or more levels of A V block [20] an indication to reduce or to discontinue the digitalis.

More difficult is the recognition of the two regions of block if second degree block of Type I exists at the lower level and results in an irregular ventricular response[10] (Fig 13) The diagnosis depends on (1) identification of typical Wenckebach periods during the irregular ventricular activity and (2) the comparison of irregular cycle lengths with ventricular cycles in portions of the record showing a rapid and regular ventricular rate. The concept of two regions of block with different conduction ratios is also helpful in unravelling the bases for the irregular ventricular rate in atrial flutter

Such multiple areas of block in the A V junction can differ not only in degree but also in direction as illustrated in Fig 14 Here the 2 1 exit block[27, 28] of the junctional pacemaker which is responsible for the extreme slowing of the ventricular rate on May 5 does not prevent retrograde penetration of A-V junctional tissues by

a premature ventricular impulse. Hence the lower region of block is either subject to a supernormal phase of conduction—an aspect discussed below in the section on A-V block—or the 2:1 block is only unidirectional and antegrade.

Tendency to unidirectional conduction seems to be a particular property of the A-V junction as evidenced by the failure of junctional impulses to be retrograde conducted to the atria in contrast to the

Fig. 14. ECG's of an 80-year-old woman with arteriosclerotic heart disease. The records are mounted in reverse order for purposes of presentation. Atrial fibrillation with complete A-V dissociation. On 5-5 the slow ventricular rate is caused by a 2:1 antegrade exit block in the lower A-V junction. Retrograde discharge of the junctional pacemaker by a ventricular premature impulse is revealed (see diagram) by the subsequent prolongation of the apparent junctional interval to 2.90 sec. (see text for details).

ready occurrence of ventricular captures by sinus impulses in straightforward cases of incomplete A-V dissociation. Fig. 15 shows a somewhat more complex situation of a double junctional tachycardia.[8,10] A region of unidirectional conduction separates the two pacemakers. This region cannot be entered by retrograde impulses from the lower pacemaker, but does permit occasional capture of the ventricles by the slower upper one which controls the atria. Sometimes, however, especially in advanced A-V block, it is the atria that can be partially or completely captured by retrograde idioventricular impulses while antegrade conduction is impaired or impossible.[11,12] This is illustrated in Figs. 16 and 20 (on October 26).

Reciprocal beating (ventricular and atrial echos). When temporal dispersion of refractoriness occurs in conjunction with areas of unidirectional block in some fibers of the conducting system, the stage is set for a re-entry process.[9,11,12] In the specific case of the A-V junction, this is called reciprocal beating by clinicians[12,14,16] and echo beats by the physiologists.[11,16,18] In clinical ECG's the problem then may arise of distinguishing reciprocal beating in junctional rhythm from ventricular captures in certain forms of incomplete A-V dissociation. Indeed the two may occur in the same record, as illustrated by Fig. 17. It shows two portions of a long record obtained from a patient with double

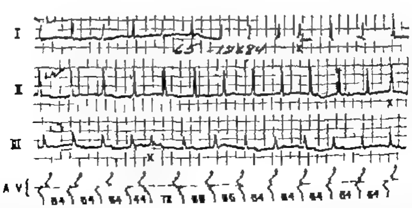

Fig. 15. ECG's of a 42-year-old woman with malignant hypertension taken while the patient was receiving digitalis. Double A-V junctional tachycardia causing incomplete A-V dissociation. The broken horizontal line in the diagram drawn through level A-V indicates a region of unidirectional block permitting capture of the ventricles by the upper junctional pacemaker (indicated in the record by X). This in turn transiently slows (depresses) the discharge rate of the lower pacemaker.

A-V junctional tachycardia. On the basis of the regular atrial activity, the early beats in the lower panel represent ventricular captures by the upper junctional pacemaker; conversely, the upper panel illustrates reciprocal beating which is identified by the irregular timing and prematurity of retrograde P waves sandwiched into the short ventricular cycles.

At the present time no agreement has been reached between physiologists and clinical observers whether an ectopic impulse travelling slowly in reverse direction through the A-V junction must reach

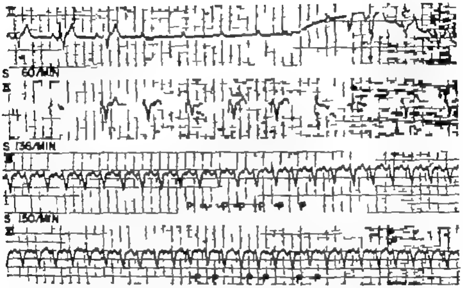

Fig. 16. ECG of 33-year-old man with Stokes-Adams disease. Unidirectional A-V block (Type II antegrade and Type I retrograde). The first strip shows a prolonged period of ventricular asystole terminated by two ventricular ectopic beats before A-V conduction is resumed. Note constancy of P-R intervals of conducted beats. In the second strip such intermittent periods of asystole are prevented by the occurrence of responses to transvenous artificial pacemaker whose discharge rate (*S*) was set at 60 per minute. Retrograde V-A conduction (*P*) occurs with sufficiently long P-R distances.[10] When the ventricular stimulator rate was increased to 136 per minute (third strip) every artificial impulse reached the atria at a constant R-P interval of 0.24 sec. With further acceleration of the stimulation rate to 150 *per minute* 3:2 *response of the atria develops with* Wenckebach periods of the retrograde conduction, R-P increasing to 0.26 sec in the second beat of the group. The region responsible for the Type II antegrade block is probably distal to that of Type I retrograde block.

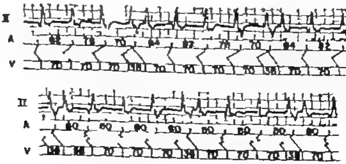

Fig. 17. ECG showing double A-V junctional tachycardia. The upper record shows reciprocal beating in junctional tachycardia with delayed retrograde conduction. The lower one shows double junctional tachycardia with incomplete A-V dissociation (see Fig. 15). The two strips were recorded in rapid succession (courtesy Dr. F. Barrera) (see text).

atrial level before it can be reflected back to the ventricles. With the exception of one study[74] experimental data indicate the complete traversion of the A V path for the occurrence of a ventricular echo.[88, 91, 166, 169] Yet clinical ECG s are on record[9, 13, 41, 43, 96] which strongly suggest that re-entry takes place within the A V junction such records, notably instances of ventricular echos following ventricular premature systoles,[43, 96] suggest that reciprocal beating may also be present when the sinus P wave—and not a retrograde P—is sandwiched between the ectopic beat with (concealed) retrograde conduction and the beat following it. The reverse, atrial reciprocal beating without activation of the ventricles (concealed antegrade re entry in the A V junction) has been established both in man[99] and in the experimental animal.[73, 88]

Re-entry in the A V junction is thus a manifestation of a longitudinal dissociation in the function of specific fibers and may involve antegrade pathways to the ventricles as well as retrograde pathways to the atria. As shown by Fig 18 some arrhythmias which appear complex can be readily resolved on this basis. In this instance of incomplete A V dissociation caused by a nonparoxysmal A V junctional tachycardia the regular sequence of the ectopic beats is disturbed by pairs of ventricular captures, the first of which has a prolonged P R interval Yet the distance between the capture beats is not shorter as expected but 0 12 to 0 14 second longer than the junctional cycle of 0.86 second

Fig 18 An ECG of a 47 ear-old man with rheumatic heart disease. Incomplet A-V dissociation due to nonparoxysmal j nctional tachycardia. Slow antegrade conduction of ventricular captures permits partial re-entry in the A V j nction (ttempts at trial echos) revealed by postponement of the next spontaneous A V junctional discharge (see text).

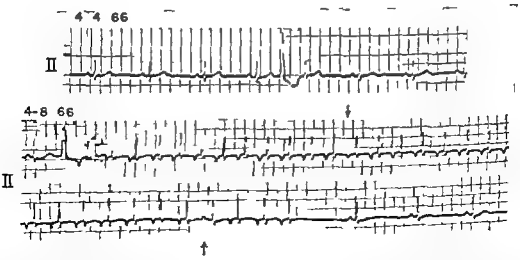

Fig 19 ECG s of a 78-year-old woman who developed paroxysmal tachycardia on 4-4-66 during a surgical procedure. On 4-4 delayed retrograde conduction of a ventricular premature beat permits A V junctional re-entry and causes single reciprocal beat. On 4-8 this reciprocation continues w th alternating entricular and atrial echos. How ever occasionally sinus impulse participates (↓) or predominates (↑) in trial activation.

In order to account for this failure of a junctional beat to occur on time a reversal of the slowly conducted sinus impulse can be postulated to occur somewhere within the A V junction, distal from the site of the ectopic pacemaker (concealed re-entry).[86] This attempted atrial echo while not reaching the atrial level, discharges the junctional pacemaker on its way and thereby postpones its next spontaneous firing—permitting one more capture of the ventricles by a sinus impulse as indicated in the diagram.

When re-entry in the A V junction is bidirectional that is, an atrial echo follows a ventricular echo or vice versa, the process may become self perpetuating continue for some time, and be the source of paroxysms of supraventricular tachycardia[69,77] as illustrated in Fig 19 In the record of April 4 a ventricular premature beat appears to be interpolated in the long sinus cycle. However the P wave buried in its ST T is distinctly premature, the subsequent sinus cycle is prolonged and shifted and the distance of the two supraventricular beats that border the premature ventricular complex is shorter than the sinus cycle All this indicates that the premature ventricular impulse during prolonged retrograde conduction to the atria has re-entered the A V junction to produce a single ventricular echo (reciprocal) beat. A similar event is seen at the start of the record of April 8. Here however the mechanism continues as a circus movement within the A V junction with 28 consecutive and alternating offsprings to the atria and ventricles until it stops spontaneously Two P waves within this paroxysm indicated by arrows differ from the other frankly inverted ones. Both are atrial fusion beats in the upper strip a retrograde, in the lower strip an antegrade (sinus) impulse predominantly activates the atria Thus, the record reveals how a clearly supraventricular type of paroxysmal tachycardia may be initiated by an ectopic beat of ventricular origin.[7,49]

A V block. One of the unsolved problems which has concerned clinical cardiologists[1,31,37,43] and more recently physiologists[149] is the mechanism of the rarer variety of second degree A V block of the Mobitz type (Type II).[78] This is illustrated in Fig 20 (upper panel of September 16) In contrast to the usual pattern observed during Wenckebach periods, dropped ventricular beats occur without forewarning that is, without preceding and progressive prolongation of the P R interval As in this instance, the majority of cases of

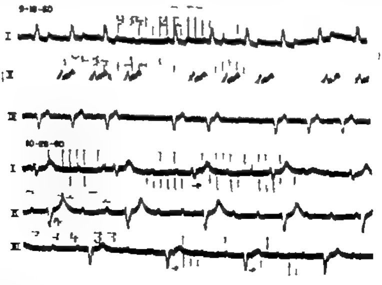

Fig 20 ECG' of 71-year-old man with syncopal attacks. A Type II second degree A V block associated with LBBB recorded on 9-16 has progressed ten days later to unidirectional A V block with complete (P) and partial (P') captures of the atria by an idioventricular pacemaker (see text).

Type II block are associated with a bundle branch block (BBB) Moreover the combination of BBB with Type II A V block advances sooner or later to incomplete or complete A V dissociation[15,37,38] as is shown in the lower panel of Fig 20 These observations supported by anatomical data[14,38] lead us to believe that in many cases of *Type II A V block* the lesions responsible for the progressive A V conduction disturbance are located not in the A V node or His bundle but instead in the two main bundle branches However if this were true for the particular case illustrated in Fig 20 as well as in others that we have seen the block in one of the bundle branches could only be unidirectional Only in this way can we account for the occasional atrial captures by idioventricular impulses as seen on October 26

Another point in favor of a bilateral bundle branch lesion causing A V block is the particular electrocardiographic pattern of right bundle branch block (RBBB) with left axis deviation[99,111] (Fig 21) In such cases, existence of bilateral bundle branch lesions has been well established by the pathologists.[3] [80] This pattern of RBBB frequently precedes development of Type II or complete A V block.[99] But this does not mean that the A V junction is spared in all of these cases. For example in Fig 21 the fact that conducted and escaping automatic beats have identical contours indicates that multiple sites of impulse obstruction exist in the A V junction as well as in the two bundle branches.[112]

The common Wenckebach type of second degree A V block may also reveal some unusual varieties (Fig 22) In this instance with 4.3 and 3.2 conduction ratios the maximal increment of P R from 0 34 to 0 58 second occurs—against the rule—not in the second but in the last beat of the Wenckebach period It would appear that toward the end of a period conductivity of the A V junction is in a critical state[44] during which the atrial impulse may be stopped short, reach the ventricles with great difficulty or penetrate only partway in the direction of the ventricles—an event that is termed concealed conduction[59,67]

Concealed conduction Concealed conduction is recognized by its aftereffects upon

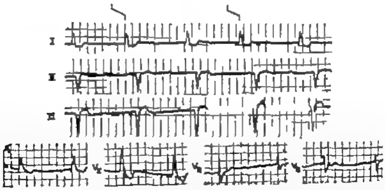

Fig 21 ECG of a 79-year-old man with atherosclerotic heart disease. Bilateral BBB combined with advanced A V block, the latter causing incomplete A V dissociation with ventricular captures (indicated by symbols above *I*) (see text)

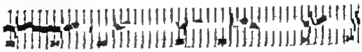

Fig 22 An ECG of 60-year-old man with recent occlusion of the right coronary artery (demonstrated at autopsy). Second degree A V block Type I revealing a critical phase of A-V conduction at the end of Wenckebach period (see text).

conduction or the formation of subsequent impulses.[11,20,71] For example, in the case of second degree A-V block, illustrated in Fig. 23, penetration of some seemingly blocked sinus impulses is evidenced by (1) the failure of subsequent P-R intervals to shorten to the optimal value of 0.20 second and (2) by blockage of two successive sinus impulses as in the middle of the record. In Fig. 24 the other manifestation of concealed A-V conduction is illustrated. In this case of intraventricular block due to old myocardial infarction a marked sinus bradycardia permits repetitive A-V junctional escape resulting in an (almost isorhythmic) A-V dissociation. However, since there is only a minor degree of A-V block—if any at all—the dissociation is incomplete. Sinus impulses occurring about 0.16 second after a junctional beat traverse the A-V junction, with delay in its lower part, and capture the ventricles (with aberrant ventricular conduction). The interval between junctional beats bordering these captures equals a prolonged ventricular interval in

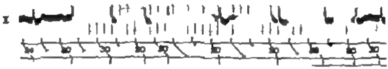

Fig. 23. An ECG of a 73-year-old woman with lymphosarcoma. Atrial (sinus) tachycardia with second-degree A-V block (2:1, 3:2, and 3:1) caused by digitalis. Concealed A-V conduction is revealed (see diagram) by its aftereffects on subsequent conduction (see text).

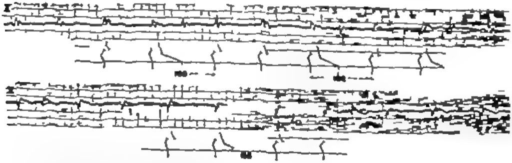

Fig. 24. ECG of a 63-year-old man with atherosclerotic heart disease. Incomplete A-V dissociation caused by repetitive A-V junctional escape in sinus bradycardia. Concealed A-V conduction is revealed by its aftereffects on subsequent impulse formation (see text).

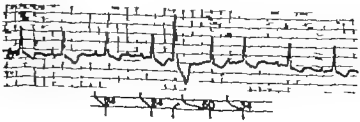

Fig. 25. An ECG of a 38-year-old woman with rheumatic heart disease. Concealed retrograde A-V conduction of an interpolated ventricular premature systole exerts its after-effect on conduction of two subsequent sinus impulses.

the lower strip—without a capture As indicated in the diagram a sinus impulse occurring at a critical point during the relative refractory phase did penetrate the lower junction deeply enough to discharge the junctional pacemaker and to postpone its next spontaneous impulse but failed to reach its destination in the ventricles. Thus in this figure and in contrast to Fig 23 concealed A V conduction is revealed by its effects on subsequent impulse formation instead of on subsequent conduction

Also to be noted in Fig 24 is the marked shortening of the ventricular cycle following the capture. This shortening indicates that most of the delay in conduction occurs below the site of the A V junctional pacemaker[115] as indicated in the diagram This delay in conduction outweighs any depressing effect of the extraneous premature discharge on the spontaneous formation of junctional impulses[17] which would tend to lengthen rather than to shorten the first automatic cycle (see Fig 15) Repetitive concealed conduction [illegible] with repetitive concealed discharge of the subsidiary pacemaker may give rise to long periods of ventricular asystole.[illegible] This appears to play a major role in digitalized patients with atrial fibrillation and flutter [illegible]

Fig 25 shows an unusual effect of concealed *retrograde* conduction of an interpolated ventricular premature beat. It is responsible for P R prolongation not merely in one but in two subsequent sinus beats. The most common and trivial example of this effect is the fully compensatory pause following a ventricular premature systole [illegible]

The practical importance of recognizing concealed conduction is illustrated in Fig 26 Atrial fibrillation with a moderately fast ventricular response on December 28 was preceded on December 24 by single and pairs of atrial premature systoles during sinus rhythm some of which were not conducted (P_1 and P_2) to account for the prolongation of the P_2-R interval we must conclude that P_1 rendered the A V junction relatively refractory On December 29 when atrial fibrillation had changed to atrial flutter the more regular rate became faster The explanation is that during the more rapid activity of fibrillation the chances for concealed conduction are improved and hence fewer atrial impulses can reach the ventricles.[14] Thus, the well known paradoxical action on ventricular rate of drugs like quinidine can be attributed to lessening of concealed conduction without implication of a supposed vagolytic action of the drug on A V conduction [14]

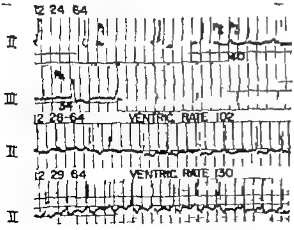

Fig 26 EGC's of 74-year-old man with atherosclerotic heart disease Concealed A V conduction revealed by its effect on conduction of atrial premature systoles (*12 24-64*) and on the ventricular rate when atrial fibrillation changes to atrial flutter (*10-28* and *29*).

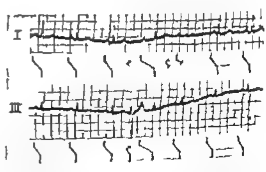

Fig 27 ECG showing pseudo-A V block of second degree. In Lead I sudden prolongation of the P R interval followed by a nonconducted P wave is caused by concealed anterograde and retrograde conduction of premature discharges of an ectopic focus in the A V junction. The evidence is given in Lead III where the same P R prolongation is induced by an interpolated premature junctional systole with only retrograde block and with aberrant conduction of the antegrade impulse

Premature formation of ectopic impulses, in conjunction with both concealed forward and concealed retrograde conduction can simulate A V block of first or second degree[66] (Fig 27) A similar effect was recently artificially produced during atrial fibrillation and described as "coupled concealed pacing"[75]

Concealed A V conduction vs double A V pathways Concealed A V conduction provides a good explanation for the ventricular bigeminy illustrated in Fig 28 which is caused by alternation of A V conduction in atrial flutter with a constant ratio of ventricular response. During a 3 1 ventricular response, the R R intervals alternate between 0 76 and 0.84 second A possible interpretation of this ventricular bigeminy is indicated in the diagram in alternate groups the first of the two nonconducted atrial impulses penetrates deeper into the A V junction. This prolongs the transmission time for the subsequent ventricular response—a mechanism that once initiated becomes self perpetuating However another explanation to be considered is the use by conducted flutter impulses of two A V junctional pathways having different conduction speeds. This problem of a dual A V transmission system invoked first by Kistin and Landowne[76] and later by Moe and co-workers[77-80] also arises in the interpretation of several other types of conduction disorders illustrated below

Double A V pathways vs supernormal A V conduction. In the case of first degree A V block during a regular sinus rhythm illustrated in Fig 29 ventricular bigeminy is attributed to alternation of A V conduction times between 0 20 and 0.32 second Paradoxically the shorter P R follows the shorter R P interval This permits two interpretations. One is the previously mentioned availability of two conduction pathways, one of which has a shorter refractory period but a slower transmission speed The other is the operation of a supernormal phase of A V conduction.[81] While the distinction between these alternatives is not possible in this instance we believe that supernormal A V conduction is operative in instances such as that illustrated in Fig 30 These records were obtained from a patient with a recent posterior and atrial infarction who de

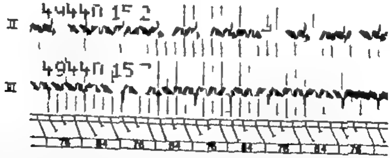

Fig. 28 ECG of 69-year-old man admitted for syncopal attacks [illegible] taken while the patient was receiving digitalis. Ventricular bigeminy in atrial flutter with overt 3 1 and attempted 3 2 ventricular responses. The alternation in the ventricular cycles is attributed to deeper penetration of the A V junction by the second atrial impulse in alternate groups (see diagram).

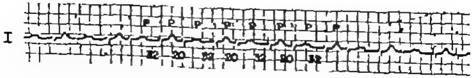

Fig 29 An ECG of 54-year-old man with ischemic heart disease Ventricular bigeminy due to "paradoxical alternation of P R intervals in regular atrial tachycardia (see text).

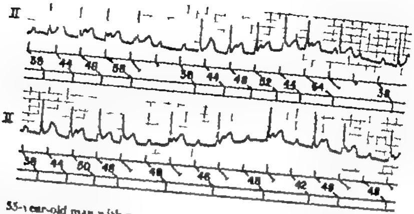

Fig 30 ECG of 55-year-old man with recent posterior wall and trial nfarction Continuous lead The last QRST of the pper strip is reproduced the first in the lower strip. Second-degree Type I A V block with block of tw successive sinus impulses (due t oncealed conduction of the first). There is alternation of A V conduction time before the dropped beat caused either by operation of a supernormal phase of A V onduction or—less likely—the vailability of t o A V pathways (see text)

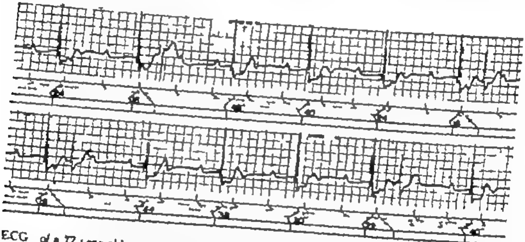

Fig 31 ECG of a 72 year-old man with Stokes-Adams syndrome Monitored continuous precordial lead. The last pair of entricular complexes of the pper trip is reproduced as the first in the lower trip The stippled area in the diagram indicates region of unidirectional block in the A V junction. The numbers are R P intervals of blocked and conducted si us impulses Ventricular captures, some w th aberra t e tric lar onduction are limited t R P inter ls of 0 16 to 0 22 sec Here the sinus impulses (oncealed onduction) rrive t a time when retrograde (con led) penet tion of entricular impulses has transiently converted the area of u idirectional oduction int one of supernormal (antegrade) conduction. Paradox all oncealed conduction facilitates subsequent onduction

veloped an atrial tachycardia with irregular ventricular responses due to a second degree A V block of Type I During some of the Wenckebach periods the initially progressive increment in A V conduction time does not continue. Instead alternation occurs in P R intervals before one or two ventricular beats are dropped [9] Paradoxically and significantly the reduction of P R from 0.52 to 0 44 second in the upper strip and from 0.50 to 0 48 second in the lower strip takes place with the shortest R P distances. The existence of a supernormal state of A V conduction is more convincingly demonstrable in instances of advanced unidirectional A V block in which early ventricular captures occur exclusively and predictably during a short time limit after an automatic ventricular beat.[84] One such case is illustrated and analyzed with the help of a diagram in Fig 31

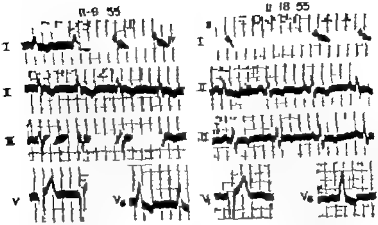

Fig. 32. ECGs of an 88-year-old man with cerebrovascular accident. Ventricular pre-excitation simulated by ectopic atrial or A-V junctional rhythm in the presence of LBBB (see text).

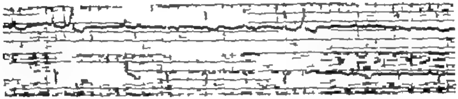

Fig. 33. ECG of an 83-year-old man with atherosclerotic heart disease. Aberrant ventricular conduction of A-V junctional escapes appearing in the pause of ventricular premature systoles.

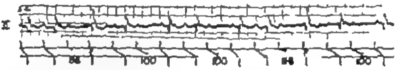

Fig. 34. An ECG of a 72-year-old woman with chronic ischemic heart disease and a left ventricular aneurysm (autopsy). Second-degree A-V block produced by digitalis. Accelerated A-V junctional escapes, identified by aberrant ventricular conduction are at times prevented by concealed A-V conduction (see text).

Ventricular pre-excitation and aberrant ventricular conduction of A-V junctional escape beats in relation to multiple A-V pathways. The uncertainty concerning the mechanism responsible for ventricular pre-excitation—the Wolff-Parkinson-White syndrome—seems today to be resolved in favor of a congenital accessory A-V connection, completely or partially bypassing the obstacle of the A-V node.[27] This has been substantiated by careful studies of anatomists[21,28] and by careful analysis of clinical records.[17,31] What remains to be established is a clearer definition of the syndrome, the possible location and functional role of the various muscle bridges found, and a more precise correlation of the anatomy with the electrocardiographic manifestations. Not every ECG that looks like pre-excitation is pre-excitation. For example, in Fig. 32, the record taken on November 9 appears to have all the classical criteria, but in the record of November 18 the P waves are upright and the P-R is normal while the abnormal ventricular complexes are unchanged. Thus, in retro-

spect the first record represents an ectopic A V junctional or low atrial rhythm in the presence of a LBBB

The functioning of an anomalous A V connection also becomes a possibility in the interpretation of minor degrees of aberrant ventricular conduction of supraventricular escape beats[44,83,116] as illustrated in Fig 33 Long ventricular intervals resulting from retrograde discharge of the sinus pacemaker by premature ventricular impulses, are terminated by escape beats that have a normal QRS duration but differ in shape from the sinus beats. Conceivably such minor degrees of ventricular aberration could be caused by an origin of the escaping impulse in or near by pass fibers running close to the normal A V junction—such as those described as paraspecific fibers by Mahaim and Winston[67] and by others.[83,84,85] [107,108] These would have to be distinguished from the massive anomalous A V connections causing the delta wave of ventricular pre-excitation which enter the ventricles more remotely from the normal junction usually at the periphery of the atrioventricular ring[43] However another interpretation of the aberration of supraventricular escapes has been proposed[118] and the problem is in need of further investigation.

Aberration of A V junctional escapes has some practical importance since it has proved to be helpful in the understanding of certain complexities in ECG's of second degree A V block An example is illustrated in Fig 34 obtained from a patient with multiple old and recent myocardial infarctions. The third beats from the beginning and from the end can be identified as A V junctional escapes not only by their coincidence with P waves and their equal cycle of 0 86 second but also by their larger R waves. On this basis the ectopic origin of these beats can be established despite longer ventricular intervals of 1 second which are terminated by conducted beats elsewhere in the record As indicated in the diagram the absence of junctional escape beats at the expected times can be attributed to deep penetration (concealed conduction) into the A V junction of some of the blocked sinus impulses. Furthermore, the record clearly reveals the double functional involvement

Table II Mechanisms involved in A V junctional arrhythmias

Established	*Problematic*
A V dissociation with and without A-V block	Bilateral bundle branch block as cause of A-V block
A V junctional parasystole	
Double and unidirectional A V block	Variant of Type I second degree A V block
Reciprocal beating of atria and/or ventricles	Alternation of A V conduction
Concealed A V conduction	Multiple A V pathway

of A V junctional tissues by the recent infarction (and/or digitalis) (1) depression of conduction as manifested by the second degree A V block and (2) acceleration of impulse generation as revealed by the abnormally high escape rate of 70

Conclusion

The nine items enumerated in the introduction can be rearranged according to established and supposed mechanisms as follows and as in Table II

On firm grounds are the causes and variants of A V dissociation A V junctional parasystole multiple regions of block and unidirectional block in the A V junction reciprocal beating of atria and ventricles and concealed A V conduction

Problematic and in need of further investigation remain bilateral bundle branch block as the cause of complete A V block and of Type II second degree A V block, variants of Type I A V block alternation of A V conduction and the role of multiple pathways in the A V junction.

REFERENCES

1 Alanis, J Propagation of impulses through the specialized tissues of the mammalian heart, *In* Paes de Carvalho, A., De Mello, W C., and Hoffman, B. F editors: The specialized tissues of the heart, Amsterdam, 1962, Elsevier Press, Inc., pp. 175-201

2. Beroaln-Santander M, Pick, A., and Langendorf R. A-V conduction in auricular flutter. Circulation 2:604, 1950.
3. Blondeau M., Rizzon, P. and Lenègre, J. Les troubles de la conduction auriculo-ventriculaire dans l'infarctus myocardique récent. I. Étude clinique. Arch. mal. Coeur 54:1092, 1961.
4. Blondeau, M., Rizzon, P. and Lenègre, J. Les troubles de la conduction auriculo-ventriculaire dans l'infarctus myocardique récent. II. Étude anatomique. Arch. mal. Coeur 54:1104, 1961.
5. Carleton, R. A. and Graettinger, J. S. Evidence of concealed atrioventricular conduction in man, Circulation 34:756, 1966.
6. Castellanos, A., Azan, L., and Calviño, J. M. Dissociation with interference between two pacemakers within the A-V conducting system, Am. Heart J. 56:562, 1958.
7. Cohen, J. Paroxysmal tachycardia precipitated by atrial or ventricular premature systoles, In Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 302-311.
8. Cranefield, P. F., Hoffman, B. F., and Paes de Carvalho, A. Effects of acetylcholine on single fibers of the atrioventricular node, Circulation Res. 7:19, 1959.
9. Cutts, F. B. Reciprocal rhythm in a patient with congenital heart disease, Am. Heart J. 14:71, 1937.
10. Daggett, W. M., and Wallace, A. G. Vagal and sympathetic influences on ectopic impulse formation, In Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 64-73.
11. De Almeida, D. F. Histological aspects of the atrio-ventricular node of the rabbit heart, In Paes de Carvalho, A., De Mello, W. C., and Hoffman, B. F., editors: The specialized tissues of the heart, Amsterdam, 1961, Elsevier Press, Inc., pp. 134-141.
12. DeHaan, R. L. Differentiation of the atrioventricular conducting system of the heart, Circulation 24:458, 1961.
13. Dohi, I., Dohi, Y., Tada, T., Mita, Y., Yoshida, K., Mitsuura, Y., Maruyama, R., Koyama, S., and Tsuketani, T. Experimental studies upon the reciprocal rhythm, Jap. Heart J. 1:275, 1960.
14. Donoso, E., Adler, L. N., and Friedberg, C. K. Unusual forms of second-degree atrioventricular block including Mobitz Type II block, associated with the Morgagni-Adams-Stokes syndrome, Am. Heart J. 67:150, 1964.
15. Dressler, W., and Jonas, S. T. Experimental production of A-V dissociation with ventricular captures by use of an internal pacemaker in patients with A-V block, Am. J. Cardiol. 10:547, 1962.
16. Drury, A. N. Paroxysmal tachycardia of A-V nodal origin exhibiting retrograde heart block and reciprocal rhythm, Heart 11:405, 1924.
17. Durrer, D., and Roos, J. P. Epicardial excitation of the ventricles in a patient with Wolff-Parkinson-White syndrome (type B), Circulation 35:15, 1967.
18. Epstein, E. J., Coulshed, N., McKendrick, C. S., Clarke, J., and Kearns, W. E. Artificial pacing by electrode catheter for heart block or asystole complicating acute myocardial infarction, Brit. Heart J. 28:546, 1966.
19. Fleischmann, P. The latent and manifest reciprocation mechanism in lower atrioventricular nodal rhythm coexistent with auricular rhythm, Acta cardiol. 6:163, 1951.
20. Gerbaux, A., and Lenègre, J. Observations sur les rhythmes à double commande (stimulation par électrostimulation) constatés après implantation d'un stimulateur interne pour maladie d'Adams-Stokes, Arch. mal. Coeur 57:286, 1964.
21. Gilchrist, A. R. Clinical aspects of high-grade heart block, Scot. M. J. 3:53, 1958.
23. Giraud, G., Latour, H., and Puech, P. L'électrocardiographie du sinus coronaire. 2ème partie. Étude électrocardiographique endocavitaire des dérythmies du sinus coronaire chez l'homme. Arch. mal. Coeur 47:1008, 1954.
24. Girard, G., Puech, P., Latour, H., and Hertault, J. Variations de potentiel liées à l'activité du système de conduction auriculo-ventriculaire chez l'homme. Arch. mal. Coeur 53:757, 1960.
25. Goodman, R. M., and Pick, A. An unusual type of intermittent A-V dissociation in acute rheumatic fever, Am. Heart J. 61:259, 1961.
26. Gubbay, E. R., and Corrado, A. M. Retrograde conduction and fourth degree dissociation in heart block, Am. Heart J. 68:166, 1964.
27. Hayashi, K. An electron microscope study on the conduction system of the cow heart, Jap. Circulation J. 26:765, 1962.
28. Hoffman, B. F. The genesis of cardiac arrhythmias, Progr. Cardiovas. Dis. 8:319, 1966.
29. Hoffman, B. F., Cranefield, P. F., and Stuckey, J. H. Concealed conduction, Circulation Res. 9:194, 1961.
30. Hoffman, B. F., and Cranefield, P. F. The physiological basis of cardiac arrhythmias, Am. J. Med. 37:670, 1964.
31. Hoffman, B. F., Moore, E. N., Stuckey, J. H., and Cranefield, P. F. Functional properties of the atrioventricular conduction system, Circulation Res. 13:308, 1963.
32. Jackson, A. E., and Bashour, F. A. Cardiac arrhythmias in acute myocardial infarction. I. Complete heart block and its natural history, Dis. Chest 51:31, 1967.
33. James, T. N. Morphology of the human atrioventricular node, with remarks pertinent to its electrophysiology, Am. Heart J. 62:756, 1961.
34. James, T. N. The specialized conducting tissue of the atria, In Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy

of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc. pp. 97-106.
35. Kaplan, B., Pick, A., and Pirani, C. L.: Clinical pathologic conference, Am. Heart J. 73:245, 1967.
36. Katz, L. N., and Pick, A.: Clinical electrocardiography. I. The arrhythmias, Philadelphia, 1956, Lea & Febiger Publishers.
37. Kaufmann, J. G., Wachtel, F. W., Rothfield, E., and Bernstein, A.: The association of complete heart block and Adams-Stokes syndrome in two cases of Mobitz type of block, Circulation 23:253, 1961.
38. Kawamura, K.: Electron microscope studies on the cardiac conduction system of the dog. II. The sinoatrial and atrioventricular nodes, Jap. Circulation J. 25:973, 1961.
39. Kistin, A. D.: Observations on the anatomy of the atrioventricular bundle (bundle of His) and the question of other muscular atrioventricular connections in normal human hearts, Am. Heart J. 37:849, 1949.
40. Kistin, A. D., and Landowne, M.: Retrograde conduction from premature ventricular contractions, a common occurrence in the human heart, Circulation 3:738, 1951.
41. Kistin, A. D.: Mechanisms determining reciprocal rhythm initiated by ventricular premature systoles: multiple pathways of conduction, Am. J. Cardiol. 3:365, 1959.
42. Kistin, A. D.: Retrograde conduction to the atria in ventricular tachycardia, Circulation 24:236, 1961.
43. Kistin, A. D.: Multiple pathways of conduction and reciprocal rhythm with interpolated ventricular premature systoles, Am. Heart J. 65:162, 1963.
44. Kistin, A. D.: Atrioventricular junctional premature and escape beats with altered QRS and fusion, Circulation 34:740, 1966.
45. Kistin, A. D.: Ventricular tachycardia and esophageal leads, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc. pp. 274-284.
46. Kistin, A. D.: Problems in the differentiation of ventricular arrhythmias from supraventricular arrhythmia with abnormal QRS, Progr. Cardiovas. Dis. 9:1, 1966.
47. Langendorf, R.: Concealed A-V conduction: The effect of blocked impulses on the formation and conduction of subsequent impulses, Am. Heart J. 35:542, 1948.
48. Langendorf, R.: Alternation of A-V conduction time, Am. Heart J. 55:181, 1958.
49. Langendorf, R., Katz, L. N., and Simon, A. J.: Reciprocal beating initiated by ventricular premature systoles, Brit. Heart J. 6:13, 1944.
50. Langendorf, R., and Mehlman, J. S.: Blocked (nonconducted) A-V nodal premature systoles imitating first and second degree A-V block, Am. Heart J. 34:500, 1947.
51. Langendorf, R., and Pick, A.: Concealed conduction. Further evaluation of a fundamental aspect of propagation of the cardiac impulse, Circulation 13:381, 1956.
52. Langendorf, R., and Pick, A.: Approach to the interpretation of complex arrhythmias, Progr. Cardiovas. Dis. 2:706, 1960.
53. Langendorf, R., and Pick, A.: Causes and mechanisms of ventricular asystole in advanced A-V block, in Surawicz, B., and Pellegrino, E. D., editors: Sudden cardiac death, New York, 1964, Grune & Stratton, Inc., pp. 97-107.
54. Langendorf, R., Pick, A., and Katz, L. N.: Ventricular response in atrial fibrillation. Role of concealed conduction in the A-V junction, Circulation 32:69, 1965.
55. Langendorf, R., Pick, A., Edelist, A., and Katz, L. N.: Experimental demonstration of concealed A-V conduction in the human heart, Circulation 32:386, 1965.
56. Langendorf, R., Simon, A. J., and Katz, L. N.: A-V block in A-V nodal rhythm, Am. Heart J. 27:209, 1944.
57. Leading article: Arrhythmias after myocardial infarction, Brit. M. J. 1:715, 1967.
58. Lenègre, J.: Etiology and pathology of bilateral bundle branch block in relation to complete heart block, Progr. Cardiovas. Dis. 6:409, 1964.
59. Lenègre, J.: Bilateral bundle branch block, Cardiologia 48:134, 1966.
60. Lepeschkin, E.: The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Progr. Cardiovas. Dis. 6:445, 1964.
61. Lev, M.: The normal anatomy of the conduction system in man and its pathology in atrioventricular block, Ann. New York Acad. Sc. 111:817, 1964.
62. Lev, M.: The pathology of complete atrioventricular block, Progr. Cardiovas. Dis. 6:317, 1964.
63. Lev, M.: Anatomic considerations of anomalous A-V pathways, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 665-670.
64. Lev, M., Leffler, W. B., Langendorf, R., and Pick, A.: Anatomic findings in a case of ventricular pre-excitation (WPW) terminating in complete atrioventricular block, Circulation 34:718, 1966.
65. Lev, M., and Unger, P. N.: The pathology of the conduction system in acquired heart disease. I. Severe atrioventricular block, Arch. Pathol. 60:502, 1955.
66. Linn, H., and Pick, A.: Anteroseptal myocardial infarction developing in stages, Dis. Chest 43:644, 1963.
67. Mahaim, I., and Winston, M. R.: Recherches d'anatomie comparée et de pathologie expérimentale sur les connexions hautes d. faisceau de His-Tawara, Cardiologia (Basel) 5:189, 1941.
68. Marriott, H. J. L.: Atrioventricular synchronization and accrochage, Circulation 14:38, 1956.

69. Marriott, H. J. L. Nodal mechanisms with dependent activation of atria and ventricles, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 412-418.
70. Medrano, G. A., De Michell, A., and Sodi-Pallares, D. Les potentiels des structures spécifiques du coeur et leurs relations chronologiques chez le chien, Acta cardiol. 17:731, 1962.
71. Meek, W. J., and Evster, J. A. E. Experiments on the origin and propagation of the impulse of the heart. III. The effect of vagal stimulation on the location of the pacemaker, the location of the pacemaker in auriculo-ventricular rhythm and the effect of vagal stimulation on this rhythm, Heart 5:227, 1914.
72. Mendez, C., and Moe, G. K. Demonstration of a dual A-V nodal conduction system in the isolated rabbit heart, Circulation Res. 19:378, 1966.
73. Meredith, J., and Moe, G. K. Excitability of A-V junctional tissue, Fed. Proc. 26:593, 1967.
74. Mignone, R. J., and Wallace, A. G. Ventricular echoes. Evidence for dissociation of conduction and re-entry within the A-V node, Circulation Res. 19:638, 1966.
75. Miyauchi, A. Electrical events in specialized fibers of a mammalian right atrium. Part II. A-V node, Jap. Heart J. 3:476, 1962.
76. Mobitz, W. Über die unvollständige Störung der Erregungsüberleitung zwischen Vorhof und Kammer des menschlichen Herzens, Ztschr. ges. Exper. Med. 41:180, 1924.
77. Moe, G. K., and Abildskov, J. A. Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart, Circulation Res. 14:447, 1964.
78. Moe, G. K., Abildskov, J. A., and Mendez, C. An experimental study of concealed conduction, Am. Heart J. 67:338, 1964.
79. Moe, G. K., Cohen, W., and Vick, R. L. Experimentally induced paroxysmal A-V nodal tachycardia in the dog, Am. Heart J. 65:87, 1963.
80. Moe, G. K., Mendez, C., and Han, J. Some features of a dual A-V conduction system, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 361-372.
81. Moe, G. K., and Mendez, C. The physiologic basis of reciprocal rhythm, Progr. Cardiovas. Dis. 8:461, 1966.
82. Moe, G. K., Preston, J. B., and Burlington, H. Physiologic evidence for a dual A-V transmission system, Circulation Res. 4:357, 1956.
83. Moore, E. N. Atrioventricular nodal transmission of premature impulses, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 353-360.
84. Moore, E. N.: Microelectrode studies on retrograde concealment of multiple premature ventricular responses, Circulation Res. 20:88, 1967.
85. Moore, E. N. Observations on concealed conduction in atrial fibrillation, Circulation Res. 21:201, 1967.
86. Moore, E., Jomain, S. L., Stuckey, J. H., Buchanan, J. W., and Hoffman, B. F. Studies on ectopic atrial rhythms in dogs, Am. J. Cardiol. 19:676, 1967.
87. Nagata, T. An experimental study on the conduction of excitation in the A-V nodal region, Jap. Circulation J. 30:1507, 1966.
88. Patten, B. M. The development of the sinoventricular conduction system, Univ. Michigan Med. Bull. 22:1, 1956.
89. Paes de Carvalho, A., and de Almeida, D. F. Spread of activity through the atrioventricular node, Circulation Res. 8:801, 1960.
90. Paes de Carvalho, A. Excitation of the atrioventricular node during normal rhythm. Effects of acetylcholine, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 341-352.
91. Paulk, E., and Hurst, J. W. Complete heart block in acute myocardial infarction. A clinical evaluation of the intracardiac bipolar catheter pacemaker, Am. J. Cardiol. 17:695, 1966.
92. Pick, A. Parasystole, Circulation 8:243, 1953.
93. Pick, A. Aberrant ventricular conduction of escape beats. Preferential and accessory pathways in the A-V junction, Circulation 13:702, 1956.
94. Pick, A. A-V dissociation. A proposal for a comprehensive classification and consistent terminology, Am. Heart J. 66:147, 1963.
95. Pick, A. Electrocardiographic features of exit block, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 469-475.
96. Pick, A., and Dominguez, P. Non-paroxysmal A-V nodal tachycardia, Circulation 16:1022, 1957.
97. Pick, A., and Katz, L. N. Disturbances of impulse formation and conduction in the preexcitation (WPW) syndrome—their bearing on its mechanism, Am. J. Med. 19:759, 1955.
98. Pick, A., and Langendorf, R. A case of reciprocal beating with evidence of repetitive and blocked re-entry of the cardiac impulse, Am. Heart J. 40:13, 1950.
99. Pick, A., and Langendorf, R. Approaches to the diagnosis of complex A-V junctional mechanisms, in Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 427-433.
100. Pick, A., and Langendorf, R. Differentiation

of supraventricular nd ventricular tachycardias, Progr Cardiovas Dis. 2:391 1960.
101 Pick, A Langendorf R. and Katz, L. N Depression of cardia pacemakers by premature imp lses, Am. Heart J 41:49 1951
102 Pick, A Langendorf R and Katz, L. N New aspects and problems nterpreting arrhythmias. Ed torial Circulation 20:997 1959
103 Pick A Langendorf R nd Katz, L. N A V nodal tachycardia w th block Circulation 24 12 1961
104 Pick, A. Landendorf R and Katz, L. N The supernormal phase of trioventricular conduction I F odamental mechanisms, Circulation 26:388, 1962.
105 Pruitt R D and Essex, H E. Potential changes ttend ng the excitation process i the trioventricular conduction system of bovine and canine hearts, Circulation Res. 8 149 1960
106 Rhodin, F A. G Del Missier P nd Reid. L C The structure of the specialized impulse conducting sy tem of the steer heart Circulation 24:349 1961
107 Robb, J S Kaylor C T and Turman, W G Study of specialized heart tissue t various tages of development of the human fetal heart, Am J Med. 5:324 1948
108. Rosenblueth, A Two processes for auriculo-entricular and ventriculo-auricular propagation of impulses in th heart, Am J Physiol, 194:495 1958.
109 Rosenblueth A Ventricular echos, Am J Physiol. 195:53 1958
110 Rossi, L Atrioventricular conduction system and nerves i the huma heart Scientia Med. Ital 3:514 1955
111 Saltzman P Linn, H and Pick, A Right h ndle branch block with left xis deviation Brit. Heart J 28 703 1966.
112 Sano, T Tasaki, M O o, M Tsuchibashi, H. Takayama, S nd Shimamoto, T Resting and action potentials in the region of the trioventricular node Proc Jap. Acad. 34:558, 1958
113. Sano, T Tasaki, M nd Shimamoto, T Histologic examination of the origin of the action potential characteristically obtained from th region bordering the trioventricular node, Circulation Res. 7 700, 1959
114 Scher A. M Direct recording from the A V conducting ystem in the dog nd monkey Science 1 1:398, 1955
115 Scher A. M Rodriguez, M I and Liikane, J The mechanism of trioventricular conduction Circulation Res. 7:54 1959
116 Scherf D Reizleit ngsstorungen im Bündel. III Nachweis einer Leitungsstörung im B ndel i klinischen Fällen Wien Arch. inn. Med. 12:327 1926.
117 Scherf D Bornemann, C and Yildiz, M A V nodal para ystole Am. Heart J 60 179 1960.
118 Scherf D and Cohen, J Atrioventricular rhythms, Progr Cardiovas. Dis. 8:499 1966
119 Scherf D and Cohen, J The trioventricular node, New York, 1964 Grune & Stratton Inc. pp. 72-93
120. Schloff L. D Adler L Donoso, E., and Friedberg, C K. Bilateral bundle branch block. Clinical and electrocardiographic aspects, Circulation 35 790 1967
121 Schott, A. Atrioventricular dissociation ith and without interference Progr Cardiovas. Dis. 2:444 1960.
122 Schubart, A. F Marriott, H. J L. and Gorten R J Isorhythmic dissociation. Atrioventricular dissociation with synchronization, Am. J Med. 24:209 1958.
123 Segal, B L., and N jmi, M Bedside diag osis of ventricular tachycardia, Dreifus, L S nd Likoff W editors Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium New York, 1966, Grune & Stratton, Inc., pp. 285-292
124 Sheiner L. B and Stock, R J Coupled pacing and coupled pacing with concealed conduction, Circ lation 34 759 1966.
125 Singer D H., Yeh B K and Hoffman, B F Aberration of supraventricular escape beats, Fed Proc. 23 158, 1964
126 Stuckey J H. and Hoffman, B. F Direct studies of the in situ specialized conducting stem Paes de Carvalho, A De Mello, W C and Hoffma B F editors The specialized tissues of the heart, Amsterdam, 1961 Elsevier Press, Inc pp 202 213
127 Toru, H Electron microscope observations of the S-A and A V nodes and Purkinje fibers of the abbit, J p. Circulation J 26:39 1962.
128 Truex, R C Bishof J K and Dow ing D F Accessory trioventricular muscle bundles. II Cardiac conduction system in ll ma specimen with Wolff Parkinson-White syndrome, Anat. Rec 137:417 1960.
129 Truex, R. C. Comparative natom nd functional considerations of the cardiac conduction system Paes de Carv lho, A De Mello, W C., nd Hoffman B F editors The specialized tissues of the heart, Amsterdam, 1961 Elsevier Press, Inc pp 22 38.
130 T uex, R C., and Smyth M Q Recent observations on the human cardiac conduction system, with special consideration of the atrioventricular node and bundle, Electrophysiology of the heart, New York, 1964 Pergamon Press, pp. 177 198.
131 Truex, R. C. Anatomic l considerations of the human trioventricular j nction, in Dreifus, L S. and Likoff W editors Mechanisms nd therapy of cardia arrhythmias, 14th Hahnemann Symposium, New York, 1966 Grune & Stratton, Inc pp. 333-340
132. Unger P N Lesser M E., Kugel, V H and Lev M The concept of masquerading bundle branch block. A lectrocardiographic-pathologic corr lation Circulation 17:397 1958
133. Vogel, J K. Differential diagnosis of supraventricular tachycardias, Dreifus L. S nd Likoff W ed'tors Mecha ism nd therapy of cardiac arrhythmias, 14th Hahne-

mann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 107-116.

134. Wallace, A. G., Cline, R. E., Sealy, W. C., Young, W. G., Jr., and Troyer, W. G., Jr.: Electrophysiologic effects of quinidine: Studies using chronically implanted electrodes in awake dogs with and without cardiac denervation, Circulation Res. 19:960, 1966.

135. Wallace, A. G., and Daggett, W. M.: Atrial re-excitation: the echo phenomenon, Am. Heart J. 68:661, 1964.

136. Walsh, T. J.: Ventricular aberration of A-V nodal escape beats: comments concerning the mechanism of aberration, Am. J. Cardiol. 10:217, 1962.

137. Watanabe, Y., and Dreifus, L. S.: Inhomogeneous conduction in the A-V node: A model for re-entry, Am. Heart J. 70:505, 1965.

138. Watanabe, Y., and Dreifus, L. S.: The site of impulse formation within the atrioventricular junction, The Physiologist 9:315, 1966.

139. Watanabe, Y., and Dreifus, L. S.: Effects of digitalis on A-V transmission, In Dreifus, L. S., and Likoff, W., editors: Mechanisms and therapy of cardiac arrhythmias, 14th Hahnemann Symposium, New York, 1966, Grune & Stratton, Inc., pp. 373-383.

140. Watanabe, Y., and Dreifus, L. S.: Second degree atrioventricular block, Cardiovascular Res. 1:150, 1967.

141. White, P. D.: Un cas de dissociation auriculo-ventriculaire complète avec réduction transitoire à moitié de la fréquence ventriculaire, Arch. mal. Coeur 11:332, 1918.

142. Winternitz, M., and Langendorf, R.: Auriculoventricular block with ventriculo-auricular response, Am. Heart J. 27:301, 1944.

143. Zahn, A.: Experimentelle Untersuchungen über die Reizbildung und Reizleitung im Atrioventrikularknoten, Arch. ges. Physiol. 151:247, 1913.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julian Frieden

Surgical treatment of valvular heart disease

Part V. Prosthetic replacement of the mitral valve

CURRENT STATUS

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Prosthetic replacement of the mitral valve first became possible with the introduction of the ball-valve prosthesis by Starr and Edwards[1] in 1961. In the seven years since this historic achievement over 15,000 mitral prostheses have been sold by the Edwards Laboratories, well indicating the widespread need for prosthetic replacement. With experience, the risk of operation has progressively decreased. In 1967, Starr and associates[2] reported personal experience with 278 patients undergoing mitral valve replacement since 1960. The operative mortality rate for isolated valve replacement decreased from 50 per cent to between 7 and 22 per cent, an average of 18 per cent. Of particular significance was the fact that the operative mortality rate for multiple valve replacement was almost identical, decreasing from 28 per cent in 1962 to 12 per cent in 1967.

During this time, several other mitral prostheses have been developed and recent studies have investigated homografts and heterografts. This article will consider these different types of mitral prostheses, present indications and operative risks, and long-term prognosis and management.

Types of mitral prostheses

Ball-valve prostheses. Most experience has been with the ball-valve prosthesis originally developed by Starr and previously employed by Hufnagel in the descending aorta before extracorporeal circulation was possible. The cardiovascular service at New York University has performed over 200 mitral replacements, evaluating both ball valves and disc valves, with the author preferring the ball-valve prosthesis. A most important consideration with a ball-valve prosthesis is to select the correct size, using one in which the cage of the prosthesis can easily be accommodated in the cavity of the left ventricle. This selection is particularly crucial in patients with mitral stenosis without enlargement of the left ventricle. Most difficulties with the ball-valve prosthesis have resulted from an unduly large prosthesis in which the ventricular septum or the wall of the ventricle impinged on the cage of the prosthesis, resulting in erosion of the ventricular wall or restriction of free motion of the ball with subsequent thrombosis. The disc valve, a low-profile prosthesis, has a distinct advantage with a small ventricular cavity and is preferred for such pa-

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tients. However, even with disc valves, protrusion of muscle into the borders of the prosthesis with restriction of motion of the disc has occurred; recent designs have "muscle guards" on the prosthesis to minimize the risk of this complication. For tricuspid replacement, because of the size and contour of the right ventricular cavity, this author has preferred a disc prosthesis, although Starr has reported excellent results with the ball valve. Except for the consideration of choosing a prosthesis of appropriate size, reported experiences with disc and ball valve prostheses have not demonstrated any superiority of one type over the other.

The main problem with prosthetic valves of all types has been thromboembolism. A significant development in the past year has been the widespread introduction of prostheses which are completely covered with a porous Teflon cloth, including both the metal rim of the prosthesis as well as the metallic struts. In April, 1968, Braunwald and Morrow[5] reported that only one embolus had occurred following 55 valve replacements with cloth-covered valves, and Beall noted two emboli after 176 replacements. In a series of 110 patients, Starr found 5 per cent with embolism soon after operation, but only 1 per cent subsequently. If these initial experiences are confirmed, the incidence of embolism with the cloth-covered prostheses will be in the range of 1 to 3 per cent, about one tenth of that with earlier prostheses. At the same time the cloth-covered prosthesis was introduced, the Silastic ball was replaced with a hollow steel ball, primarily because of experience with erosion or fracture of the Silastic ball with aortic prostheses. These factors are considered in more detail in the companion article in this series on *Prosthetic cardiac valves*.

A different type of ball valve prosthesis was developed by Smeloff, termed the Cutter prosthesis. In this type of prosthesis, the cage mechanism is partly in the atrium and partly in the ventricle, thus limiting the extent to which the cage extends into the ventricular cavity. A "controlled leak" is designed in the prosthesis to permit a small amount of leakage of blood when the ball is seated, hoping by this washing effect during each systolic contraction to minimize the deposition of thrombi. Although this prosthesis has had extensive clinical trial, no consistent advantage has been found over the conventional Starr Edwards prosthesis.

Disc prostheses. In these prostheses a disc, rather than a ball, is used for the mobile, occluding mechanism. With a disc, the cage enclosing the disc is much shorter than the cage in ball valves. Hence, such prostheses are termed "low profile" prostheses. Their main advantage is that they can be inserted into a ventricular cavity of small size with little risk of impingement on the surrounding ventricular wall or septum. Although the hemodynamic flow patterns are theoretically more desirable than those with a ball valve, the clinical significance of these differences has not been apparent. The incidence of thromboembolism has been similar to that with a ball valve. Theoretically, less force is required to hold a disc valve in position because the force of impact of the disc against the seating ring of the prosthesis is less than that with a ball valve prosthesis. A disadvantage of the disc prosthesis is that free rotation of the disc may not occur and result in unequal wear, whereas the randomly spinning ball of a ball valve prosthesis is more immune to wear.

Several different types of disc prostheses have been developed, including the Hufnagel prosthesis, the Kay-Shiley prosthesis, the Earle Kay prosthesis, the Cross-Jones prosthesis, and more recently the Beall prosthesis. No significant clinical differences have been reported among these different types. Most of these have recently been modified so that the metallic surfaces are completely covered with cloth.

Homograft and heterograft prostheses. With the increasing use of aortic homograft prostheses, considerable effort has been expended to develop mitral homograft prostheses. With the chordae tendineae, however, replacement of the mitral valve with a homograft is much more difficult. In April, 1968, Angell and associates[6] reported experiences with 70 patients in whom the mitral valve was replaced with a fresh aortic homograft valve, which was attached to a prosthetic ring and then sutured to the mitral annulus in an in-

verted position. Similarly, Ionescu and colleagues[7] have described 50 patients in whom a heterograft aortic valve from a pig was used in a similar manner. Although initial experiences have been satisfactory, long-term results are not available.

Operative indications and hazards

Indication. At present, operation should be recommended only for seriously disabled patients, particularly individuals who are unable to work and despite intensive medical therapy are developing progressive signs of congestive heart failure. The reason for restricting prosthetic replacement to advanced forms of heart disease is that the combined operative and late mortality rate following prosthetic replacement of the mitral valve has been about 25 per cent. The 28 per cent average mortality rate in 155 patients reported by Starr has already been mentioned. In 100 patients reported by Morrow and associates,[8] the operative death rate was 17 per cent and late deaths were 7 per cent, a total of 24 per cent. With improvements in operative technique, operative risk has decreased to about 10 per cent. Hopefully, the cloth-covered prostheses will decrease the late risk from thromboembolism, but significant long-term data are not yet available. Only when prostheses are available with a negligible risk of thromboembolism should operation be recommended in earlier stages of the disease.

Operative hazards. At operation, the main hazards are air embolism and hemorrhage from friable calcified tissues. With increasing experience, deaths from either of these causes have progressively decreased. Following operation, the low cardiac output syndrome has similarly become less frequent, most likely because of careful transfusion following operation to keep left atrial pressure elevated to 15 to 20 mm. Hg. Arrhythmias are one of the more frequent postoperative complications and require intensive observation and therapy with digitalis, potassium, procaine amide, and selective electrical pacing of the heart with a pacemaker wire implanted at the time of operation. Pulmonary, renal, and hepatic complications of minor degree are frequently seen but are seldom fatal. Thromboembolism may occur in the early postoperative course, but again is infrequent if anticoagulation is begun four to five days after operation. Infection has fortunately become rare with the intensive use of large amounts of bactericidal antibiotics during and following operation. Most of the patients receive Staphcillin in large amounts during operation and for one month afterward. In the past six years, infection of the prosthetic valve (organism, *Candida albicans*) occurred in only one patient.

Long-term prognosis and management

It is important to realize that the mortality risk in the two years following discharge from the hospital is about equal to that associated with operation. This well emphasizes the importance of careful long-term medical management following prosthetic replacement, considering surgical replacement of a mitral valve as only one phase in the treatment of the patient with valvular disease. Many causes of late deaths can probably be avoided by early detection and treatment of complications. In the report by Starr, about one half of the late deaths were due to the prosthesis, either from thromboembolism, detachment of the prosthesis, or other complications. In about one half of the patients, however, death was apparently due to an arrhythmia or to myocardial disease, for only myocardial fibrosis was found at post-mortem examination. In seven late deaths reported by Morrow and associates, two were due to infection of the prosthetic valve and all others were related to malfunction of the prosthesis.

In long-term management of the patient with a prosthetic mitral valve, three areas of therapy should be considered.

1. *Anticoagulation.* This author's preference is to maintain anticoagulation permanently, administering Coumadin (sodium warfarin) daily to keep the prothrombin time about twice the normal rate. Anticoagulant therapy is not without its hazard, however, because of the risk of hemorrhage. One death has occurred in our patients in the last two years, directly related to sodium warfarin therapy, primarily from negligence on the part of the

patient. Major hemorrhage occurred in two other patients, however, despite careful medical observation. Fortunately these subsided without serious sequelae in each instance. With the new cloth-covered prostheses, it may be found possible to stop anticoagulation after several months, at which time the prostheses should presumably be covered with a new endothelium.

When a surgical operation is performed, such as a cholecystectomy, anticoagulant therapy must be stopped for a short period of time. Our preference has been to give heparin until a few hours before operation and then to resume heparin one to two days afterward.

2. *Antibiotic therapy.* Antibiotic therapy, usually sodium methicillin (Staphcillin), is given for four to five weeks following operation. With this program bacterial infections have not occurred in the past several years. Subsequently, antibiotics are recommended if surgical procedures are performed which might induce a transient bacteremia, such as extraction of a tooth or a cystoscopic examination. Fatal endocarditis developing after such procedures has been reported by several investigators.

3. *Cardiac function.* The degree of recovery of cardiac function following prosthetic mitral replacement must be carefully evaluated by the physician over a period of several months. Such evaluation should include the presence of symptoms, regression of heart size and signs of ventricular hypertrophy on the electrocardiogram, and tolerance for the intake of sodium. An attempt should be made to correct chronic atrial fibrillation by electrical cardioversion a few weeks following operation. In patients who have been fibrillating for long periods of time, a permanent conversion to sinus rhythm can be obtained in about 30 to 35 per cent. In the group of patients reported by Starr in 1967, 63 per cent were free of all cardiac symptoms and taking a regular diet and roentgenograms had showed a dramatic reduction in cardiac size. Twenty-five per cent had mild restriction of exercise ability and did not require salt restriction. Ten per cent had persistent cardiomegaly and required permanent intensive medical therapy, obtaining little benefit from operation. In the 76 patients surviving operation reported by Morrow and associates, 47 were classified as Class I, 16 as Class II, and three as Class III. The reason for the variation in results is not known. It may be that some patients have a superimposed myocardial disease (a rheumatic myocarditis?), but in any event the response following operation is not a uniform one and must be determined by the physician over a long period of time.

If cardiac symptoms persist following operation, several possibilities should be evaluated. The most important is whether mitral insufficiency has developed from a perivalvular leak around the rim of the prosthesis, usually due to one of the sutures anchoring the prosthesis cutting through the fibrous tissue of the residual annulus. Such a diagnosis can be confirmed or excluded only by angiography of the left ventricle. It is surprising that in some patients a significant leak can be present without an audible murmur. Hence, repeat cardiac catheterization and angiography should be performed in any patient with persistent cardiac symptoms.

Other possibilities include the presence of additional valvular disease, such as aortic or tricuspid valvular disease. Rarely a serious arrhythmia can precipitate cardiac failure in the absence of other findings. An increased pulmonary vascular resistance almost always subsides following mitral replacement and is rarely a cause of persistent difficulty. Finally, when other possibilities have been excluded, the possibility of intrinsic disease of the left ventricular muscle must be considered. This is usually characterized by persistent cardiomegaly with a left ventricular end-diastolic pressure above 15 mm. Hg and absence of any signs of mitral regurgitation.

Because of the varying response of different patients to operation, the salt intake and the physical exertion of the patient should be carefully evaluated by the physician for several months following operation. This author personally has seen more than one patient in whom a sudden change in physical activity or an excessive salt intake several months fol-

lowing operation precipitated edema and cardiac failure

Summary

Extensive experience has been gained with prosthetic replacement of the mitral valve since it was first introduced by Starr in 1961. Operative mortality following prosthetic replacement has decreased to about 10 per cent, but 10 to 15 per cent of patients subsequently die in the first two years following operation either from complications related to the prosthesis or from their underlying cardiac disease. Hence, at present, operation should be recommended only for patients with progressive disability from valvular disease. Following mitral replacement about 65 per cent of patients become asymptomatic, 25 per cent have mild symptoms, and for unknown reasons about 10 per cent remain with significant disability.

A potentially very significant advance has been made in the past year with the introduction of cloth-covered prostheses, which from presently available data indicate that the incidence of thromboembolism may be decreased from the range of 20 to 25 per cent to as low as 2 to 4 per cent. This advance if confirmed may greatly liberalize future indications for mitral valve replacement. Only preliminary experiences are yet available with homograft and heterograft prostheses.

REFERENCES

1. Starr A. and Edwards, M. L. Mitral replacement Clinical experience with a ball valve prosthesis, Ann. Surg 154:726 1961
2. Starr A. Herr R. H and Wood, J A. Mitral replacement. Review of six years experience, J Thoracic & Cardiovas. Surg 54:333 1967
3. Spencer F C. Cortes, L., Marcarenhas, G Ifuku M and Koepke J Mechanism of thrombus formation upon Starr Edwards prosthetic mitral valves, Ann. Surg 165:814 1967
4. Braunwald, N S., and Bonchek, L I. Prevention of thrombus formation on rigid prosthetic heart valves by ingrowth of autogenous tissue, J Thoracic & Cardiovas. Surg 54:630, 1967
5. Braunwald N S. and Morrow A. G. Tissue ingrowth and the rigid heart valve Review of clinical and experimental experience during the past year J Thoracic & Cardiovas. Surg 56:307 1968.
6. Angell, W W Stinson, E. B Iben A B and Shumway N E Multiple valve replacement with the fresh aortic homograft, J Thoracic & Cardiovas. Surg 56:323 1968
7. Ionescu M I Wooler G. H Whitaker W Smith D R Taylor S. H and Hargreaves, M D Heart valve replacement with reinforced aortic heterografts Technique and results J Thoracic & Cardiovas. Surg. 56 333 1968.
8. Morrow A. G Oldham H N Elkins, R. C., and Braunwald, E Prosthetic replacement of the mitral valve. Preoperative and postoperative clinical and hemodynamic assessments in 100 patients, Circulation 35:962 1967

Annotations

Hemodynamic effects of ethyl alcohol in coronary heart disease

Ethyl alcohol has been used in the treatment of angina pectoris ever since its original description by Heberden. Relief or prevention of ischemic pain has been frequently described and, although Russek and his colleagues[1,2] failed to show any improvement in the exercise electrocardiograms (ECG's) of patients with coronary heart disease, alcohol has retained a place in current therapeutic advice.[3-5] Until recently attempts to study the immediate hemodynamic consequences of alcohol ingestion have been largely confined to animal experiments. The principal interest, naturally, has been in the coronary circulation but there has been little agreement about the effect of alcohol on this, or indeed on any circulatory measurement.[6-10] The explanation may lie in the varying conditions of each study or differences in the amount or route of administration of the alcohol given but, in any event, the relevance of such studies, carried out in healthy anesthetized animals, to the atherosclerotic patient is open to question.

A recent study[11] has examined the hemodynamic changes in eight patients with stable coronary heart disease after a drink of alcohol equivalent to three or four whiskies (0.5 gram of alcohol per kilogram of body weight). Observations were made initially at rest for 45 minutes after the alcohol intake and were followed by a period of graduated exercise on a bicycle ergometer. Comparison was made in each patient with identical control studies immediately beforehand. Blood alcohol concentrations rose to moderate levels in most instances and thus no clear correlation emerged between the height of blood alcohol attained and the degree of circulatory change produced. Arterial pressure dropped progressively at rest and was lower at each exercise level. Cardiac output also fell (particularly at rest) and surprisingly, therefore, the calculated peripheral resistance did not alter. Of course, this is a crude way of assessing systemic vascular response but it is probable that alcohol owes its reputation as a vasodilator to an increase in the blood flow to the skin[12] in the muscle blood flow falls and other unknown regional vascular behavior probably exist. No change occurred in the heart rate despite the influence of excitement and euphoria in several patients. Left ventricular work declined both at rest and upon effort and the tension time index fell reflecting myocardial oxygen uptake.[13] These hemodynamic events were accompanied by flattening of the T waves in left ventricular leads of the resting ECG in two subjects with S-T depression in a third. Upon effort, positive exercise changes appeared in the ECG of two other patients which had not been present during control studies. No significant alteration was observed in the amount of work required to produce angina. The conclusion was reached that alcohol was acting as a myocardial depressant.

This view of the action of alcohol is also taken by Regan and his associates.[14-16] They studied its action both in dogs[14,15] and in young alcoholic patients under investigation for fatty livers but without any sign of heart disease.[16] Alcohol reduced myocardial contractility with a fall in stroke volume (unaccompanied by an alteration in heart rate) and a small rise in left ventricular end-diastolic pressure. Coronary flow itself showed little change but its content of potassium and phosphate ions and of transaminase rose. Arterial pressure (measured in dogs only) was unaffected. They did not comment on the ECG. These changes persisted for some hours in the presence of raised blood alcohol levels. In another experiment after alcohol, their subjects responded to angiotensin infusion as if they had heart disease (although clinically they had normal hearts) by failing to increase stroke volume in answer to increments in left ventricular end-diastolic pressure. Regan and his colleagues[14,16] concluded that alcohol causes reversible myocardial injury. Interestingly, they were able to reproduce their findings in the coronary outflow after alcohol, both in animals and man, by giving parenteral hypertonic sucrose in quantities sufficient to raise the plasma osmolarity by the same amount as alcohol had done and noted (in dogs only) similar hemodynamic effects. Other work on the influence of altered plasma osmolarity on mammalian myocardium[17] supports their contention that the mechanism of myocardial depression by alcohol is an osmotic one.

While it is just possible that the changes seen in the patients with alcoholism were due to subclinical myocardial involvement, this was certainly not true of the eight patients with coronary heart disease in the most recent study all of whom were

accustomed to modest alcohol intakes only and the effect of alcohol on myocardial function is clearly ad erse. This may be of particular importance in the tiology of lcoholic cardiomyopathy but it would lso seem prudent for patients with angina to t k alcohol i moderation only.

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REFERENCES

1. Heberden W. Some accou t of disorder of the heart. M. T. Roy. Coll. Physicia 2:59 1786
2. Russek, H. I. Naegele C. F. and Regan F. D. Alcohol in the treatment of ngina pectoris, J. A. M. A. 143:355 1950
3. Russek H. I. Zohman B. L. and Dorset, V. J. Objective evaluation of coronary vasodilator drugs. Am. J. M. Sc. 229:46 1955
4. Cecil, and Loeb Textbook of med ine, ed 12, Beeson, P. B. and M Dermott W. editors. Philadelphia nd London 1967 W. B. Sa nders Company
5. Laurence D. R. Clinical pharmacology ed. London, 1963 J. & A. Churchill, Ltd.
6. Lasker N. Sherrod, T. R. and Killam K. F. Alcohol and the coronary circulation of the dog, J. Pharmacol. & Exper. Therap 113:414 1955
7. Ganz V. The acute effect of lcohol on the circulation and on the oxygen metabolism of the heart. Am. Heart J. 66:494 1963
8. Degerli, V. and Webb W. R. Alcohol cardiac function and coronary flow. S. Forum 14:252 1963
9. Lemingher D. S. Rueger R., and Beck, C. S. Effect of pentaerythritol tetra itrate amyl nitrite and alcohol on arterial blood supply t ischaemic myocard m, Am. J. Cardiol 7:533 1961
10. Willard P. W. and Horvath, S. M. Coronary circulation during and following thyl alcohol infusion Arch. Int. Pharmacodyn. 148:181 1964
11. Conway N. Haemodynamic effects of alcohol patient with coronary heart disease Proc. Brit. Cardiol Soc May 1967
12. Gillespie J. A. Vasod lator properties of alcohol, Brit. M. J. 2:274 1967
13. Sarnoff S. J. Braunwald E. Welch G. H. J. Case, R. B. Stainsby W. N. and Macruz R. Haemodynamic determinants of oxygen consumption of the heart with special reference t the tension time index, Am. J. Physiol. 192:148, 1958.
14. Regan T. J. Weisse, A. B. Oldewurtel, H. A. nd H lems, H. K. The hyperosmotic effect of ethanol nd sucrose on the left ventricle J. Clin. Invest. 43 1289 1964.
15. Regan, T. J. Koroxenidis, G. Moschos, C. B. Oldewurtel H. A. Lehan, P. H. and Hellems, H. K. Acute metabolic nd haemodynamic responses of the left ventricle t ethanol, J. Clin. I vest 45:270, 1966
16. Regan, T. J. Weisse A. B. Moschos, A. B. Lesniak, L. J. Nadim M. and Hellems, H. K. The myocardial effect of ac te nd chronic usage of ethanol in man, T. A. Am. Phys. 78:282 1965.
17. Koch Weser J. Influence of osmolarity of perfusate on contractility of mammalia myocardium, Am. J. Phy iol 201:957 1965

Idiopathic hypertrophic osteoarthropathy

Touraine-Solente-Gole syndrome

Idiopathic hypertrophic osteoarthropathy is clinical entity whose familial and hereditary occurrence ha been well documented for many years. The har acteristics are clubbing of the fingers nd toes, inter mittent swelling with or without tenderness of the large joints with periost l hypertrophy and new bone formation skin hanges of the scalp face hands, and legs with furrowing, troph and seba ceous gland overactivity and hyperhidrosis of the hands and feet. Because these findings may be present separately or together i a single individual much confusion has been accumulated over the years. The term pachydermoperiostosis ha been advocated as a descripti term for the syndrome.

Similar findings may develop in association with arious diseases. Usually in the secondary type of hypertrophic osteoarthropathy the most triking feat res are lubbing and periosteal hypertrophy. However marked kin changes may be prominent in the secondary type. The secondary type occurs most commonly in pulmonary lesion nd is called pulmonary hypertrophic osteoarthropathy by Pierre Marie. It may also occur with various tumors such as primary nd metastatic carcinoma of the lungs l tumors of the pleura nasophary x, esophagus, tomach lymphosarcoma, nd thalchemy ostomy of the heart w th gastroi testinal disorders such lcerati colitis cirrhosis, regional enteritis, and steatorrhea, nd ith subacut bacterial endocar diti thoracic aneurysm, congenital heart disease

thyroid acropachy[23] and even pregnancy.[24] Reflexes mediated through the vagi apparently cause the changes which may be reversible if the vagi are severed below the aortic arch. The increased blood flow to the bones and limbs[25] is thus reduced and accounts for the regression of the arthropathy and soft tissue swelling.[26,27] However, diminished blood flow to the clubbed fingers has been demonstrated by Rimoin[28] in idiopathic periostosis.

The primary type, idiopathic or familial form of hypertrophic osteoarthropathy (Touraine-Solente-Golé (TSG) syndrome) was observed as early as 1868[29] and again in siblings in 1888,[30] but was considered to be acromegaly because of the body and facial configuration. An autopsy of one of these cases demonstrated marked periosteal changes and new bone formation and acromegaly was thus no longer a tenable diagnosis. Isolated reports of the cutaneous changes seen in this syndrome appeared as early as 1906. In 1935 Touraine, Solente, and Golé[31] reported the first complete description of the disease as one which affected young male subjects, and was self-limited and not congenital; they called it idiopathic since no underlying disease was present. The entity was finally recognized as hereditary by Brugsch in 1941.[32] Touraine, Solente, and Golé differentiated this entity into three forms: (1) complete, (2) incomplete without involvement of the scalp, and (3) frustes when the skin features are present with minimal or no periosteal changes.

The syndrome starts usually during the adolescent period, runs a progressive course for several years, and is self-limited. Only thickened periosteum is detected early. In older individuals, periosteal and new bone formation is present. The occasional occurrence in female subjects has usually been in sisters of male patients with demonstrable pachydermoperiostosis. The differential diagnosis includes acromegaly and leprosy when the facial and scalp changes are marked, rheumatoid arthritis, Paget's disease, and luetic periostitis because of periosteal and bone changes, vitamin A intoxication, and idiopathic periosteal hyperostosis with dysproteinemia as entities producing periosteal changes.[33]

The syndrome has been observed to be transmitted in a quarter of the progeny as an autosomal recessive or not completely dominant gene. This concept was challenged by Tsoneva-Maneva and associates[34] who found an abnormal pattern of XYY chromosomes in a father and son with idiopathic hypertrophic osteoarthropathy. We have performed chromosome studies in the affected brothers and in the sons of one of them in a family with the TSG syndrome. All showed a normal sex-chromosome complement.[35] Although XYY chromosome pattern may appear in several conditions, it is quite clear that this is not the genetic mechanism by which the familial idiopathic hypertrophic osteoarthropathy is transmitted through generations. In a Letter to the Editor which has recently come to our attention, findings similar to ours were reported by Rimoin and Borgaonkar[37] who share the same opinion that abnormal chromosomes are not responsible for the familial inheritance. In the family studied by us we observed a dominant transmission: four of the living brothers showed different degree or aspects of the syndrome; only one sister was examined and disclosed no abnormalities. Since the rest of the relatives were not available for observation, we are unable to make further comments.

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REFERENCES

1. Vogl, A., and Goldfischer, S.: Pachydermoperiostosis. Primary or idiopathic hypertrophic osteoarthropathy, Am. J. Med. 33:166, 1962.
2. Hollis, W. C.: Hypertrophic osteoarthropathy secondary to upper gastrointestinal tract neoplasm, Ann. Int. Med. 66:125, 1967.
3. Huckstep, R. L., and Bodkin, P. E.: Vagotomy in hypertrophic pulmonary osteoarthropathy associated with bronchial carcinoma, Lancet 2:343, 1958.
4. Aufses, A. H., and Aufses, B. H.: Hypertrophic osteoarthropathy in association with pulmonary metastases from extrathoracic malignancies, Dis. Chest 38:399, 1960.
5. Harrison, T. R.: Principles of internal medicine, ed. 5, 1966, McGraw-Hill Book Co., Inc., page 1360.
6. Diner, W. C.: Hypertrophic osteoarthropathy. Relief of symptoms by vagotomy in a patient with pulmonary metastases from lymphoepithelioma of the nasopharynx, J. A. M. A. 181:555, 1962.
7. Perlman, M. A.: Achalasia of cardia, carcinoma of the esophagus and hypertrophic pulmonary osteoarthropathy, Brit. M. J. 1:23, 1959.
8. Singh, A., Jolly, S. S., and Bansal, B. B.: Hypertrophic osteoarthropathy associated with carcinoma of the stomach, Brit. M. J. 2:581, 1950.
9. Gorman, J. T., Schruder, [illegible] I., and O'Connor, T.: Hypertrophic osteoarthropathy. Report of a case associated with lymphosarcoma, M. Ann. District of Columbia 27:242, 1958.
10. Pascuzzi, C. A., Parkin, T. W., Bruwer, A. J., and Edwards, J. E.: Hypertrophic osteoarthropathy associated with primary rhabdomyosarcoma of the heart, Proc. Staff Meet. Mayo Clin. 32:30, 1957.
11. Buchan, D. J., and Mitchell, D. M.: Hypertrophic osteoarthropathy in portal cirrhosis, Ann. Int. Med. 66:130, 1967.
12. Means, M. G., and Brown, N. W.: Secondary hypertrophic osteoarthropathy in congenital heart disease, Am. Heart J. 34:262, 1947.

13. Gimlette, T. M. D.: Thyroid acropachy, Lancet 1:22, 1960.
14. C llen, D. R., and Maskery P. J.: Clubbing of the fingers and hypertrophic osteoarthropathy in pregnancy, Lancet 2:473, 1966.
15. Flavell, G.: Reversal of pulmonary hypertrophic osteoarthropathy by vagotomy, Lancet 1:260, 1956.
16. Mendlowitz, M.: Clubbing and idiopathic osteoarthropathy, Medicine 21:269, 1942.
17. Holling, H. E., Danielson, G. K., Hamilton, R. W., Blakemore, W. S., and Brodey, R. S.: Hypertrophic pulmonary osteoarthropathy, J. Thoracic & Cardiovas. Surg. 46:310, 1963.
18. Rimoin, D. L.: Pachydermoperiostosis (idiopathic clubbing and periostosis), New England J. Med. 272:923, 1965.
19. Friedreich, N.: Hyperostose Des Gesammten skelettes, Virchows Arch. path. Anat. 43:83, 1868.
20. Fraentzel, O.: Uber Akromegalie, Deutsche med. Wchnschr. 14:653, 1888.
21. Jadassohn, J.: Eine eigentumliche Furchung, Erweiterung und Verdick ng der Haut am Hinterkopf, IX Kongress Deutschendermatol. Gesellsch., Bern, 1906, page 452.
22. Touraine, A., Solente, A., nd Gole, L.: U syndrome osteodermopatique. La pachydermie plicaturée vec pachyperiostose des extremities, Presse med. 43:1820, 1935.
23. Brugsch, H. G.: Acropachyderma with pachyperiostitis. Report of a case, Arch. I t. Med. 68:687, 1941.
24. Goldbloom, R. B., Stein, P. B., Eisen, A., Mc Sheffrey, J. B., Brown, H. J. St. and Wiglesworth, F. W.: Idiopathic periosteal hyperostosis with dysproteinemia, New England J. Med. 274:873, 1966.
25. Tzoneva-Maneva, M. T., Bosajieva, E., and Petrov, B.: Chromosomal abnormalities in idiopathic osteoarthropathy, Lancet 1:1000, 1966.
26. Summa o, A., Shah, P., Krompotic, E., and Tashima, C.: Normal sex chromosome complement in a case of familial osteoarthropathy, Lancet 2:131, 1967.
27. Rimoin, L. D., and Borgaonkar, D. S.: Chromosomal abnormalities in idiopathic osteoarthropathy, Lancet 2:860, 1966.

Serum lipids and cerebrovascular disease

The possibility of there being an etiological connection between serum lipids and vascular disease has been most extensively studied in relation to the coronary arterial system. In the early 1950's, t was reported that the total free and esterified plasma cholesterol were elev ted in patients with coronary artery disease as compared w th normal subjects. Sometime later it was demonstrated that the ratio of α- t β-lipoprotein was less in patients with coronary artery disease than it was in healthy controls.[3,4] Finally it was established that the most sensitive indicator of lipid abnormality in coronary artery disease was the serum triglyceride level.

These observations were made on subjects with clinical evidence of established coronary disease. More important was the demonstration that the serum lipid level is raised before there are manifestations of clinical disease. The level of lipids in the serum has value therefore in predicting that a per son is likely to develop coronary arterial disease. The influence of age must, however be borne in mind because it has been shown that the triglycerides[6] and the α and β-lipoprotein fractions increase with age in normal people. As result, the significant difference between the serum lipid level of patients who have developed, or who are about to develop clinical manifestations of coronary arterial disease and of normal controls can only be shown in younger age groups. If a patient does not develop myocardial infarction, or other evidence of coronary arterial disease until later in life, t may not be possible to demonstrat that his serum lipid level is significantly different from his contemporary who is not showing clinical signs or symptoms. Even when patients are grouped, t may still be impossible to demonstrat significant difference between patients and controls in the older age groups.

The study of the relationship between serum lipids and cerebrovascular disease is even more complex because the range of disorders afflicting the cerebral arterial system is greater than that affecting the coronary arterial system. The two major pathological processes affecting the cerebral arteries are thero-sclerosis and hypertension. In typical ases the effect of these two processes can be clearly separated, the former giving rise t atheromatous lesions in large arteries such as the carotid nd vertebral, hereas the latter affects mainly the smaller arteries, producing medial hypertrophy nd leading to the formation of microaneurysms of the Charcot Bouchard type. [9] The distinction between the effect of these two processes is, however in practice less sharp for hypertension besides producing medial hypertrophy increases the number of atheromatous plaques t be found in the large cerebral essels, nd produces theroma in smaller essels than are usually involved in the nonhypertensive patient. I addition, when account is taken of the fact th t the differentiation I Ill bet een cerebral infarction consequent upon theroma nd cerebral hemorrhagic lesions

from hypertension is extremely difficult,[10,11] the complexity of the problem is clearly manifested. The comparison of serum lipid levels in patients with cerebrovascular disease or stroke illness and controls is in effect comparison between number of disorders on the one hand and controls on the other

An ttempt was made to distinguish between the effects of atheroma and hypertension by separating patients with a clinically diagnosed cerebral infarction according to their level of blood pressure. The mean serum cholesterol in the patients with diastolic blood pressure of less than *110* mm. Hg was 228 mg per 100 ml whereas in those whose diastolic was 110 mm. Hg or above, the level was 209 mg the difference falling just short of the 5 per cent level of significance. I view of the finding i coronary arterial disease that the triglyceride is more useful indication than cholesterol, the serum levels of *triglycerides, as well as total and free cholesterol,* phospholipids, and series of fatty acids was further determined in these two groups of patients,[12] but none reached the 5 per cent level of significance.

The observation that the difference between serum lipid levels of patients with coronary arterial disease and of healthy controls, which is manifest in the younger age groups, disappears with advancing age, is, however clearly relevant. Patients with stroke illness are on erage, older than patients showing signs of coronary arterial disease, hence, it might be expected that any difference between their serum lipids and those of their healthy contemporaries, which might have been present in early adult life, would ha disappeared. Evidence that this indeed is the case has recently come from the Framingham study[14] Subjects with a high serum cholesterol before 50 years of age were more liable ltimately to develop an therosclerotic cerebral infarction than those whose cholesterol was normal After the age of 50 this difference could no longer be discerned.

This tendency for significant differences between the serum lipid levels of different groups of subjects to disappear with advancing age seems to be general phenomenon. For instance, the serum triglyceride levels are significantly raised in young, obese female subjects as compared with nonobese subjects, but in the older age groups the difference was no longer apparent, the normals having, as it were *caught up.*[7,8] *Similarly serum triglycerides* and the distribution of subcutaneous fat ere found to be significa tly related in men below the age of 34 but after this age the correlation was no longer demonstrable.[16]

It seems, therefore reasonable to postulate that the level of serum lipids, particularly triglycerides, before middle age is significantly related to the subsequent development of cerebral therosclerosis, which is an important predisposing factor in the development of cerebral infarction. By the time infarction occurs, however this difference in serum lipid levels is no longer apparent, the healthy subjects having caught up with those afflicted with arterial disease.

If this postulate is established, it will raise grave problems in the field of preventive medicine. The establishment of some method of screening the population to discover those whose serum lipid level is above average in young ad lt lif would be necessary It would also be necessary to ascertain whether the reduction of the level, in those in whom it is raised, either by diet or by drugs, reduces the risk of the subsequent development of *cerebral atherosclerosis* and infarction. When it is remembered that cerebrovascular disease is the third largest cause of death in many western countries t the present time, the size of this problem needs no stress. However the first task is to ascertain the facts, which can only be done by setting up well-designed, longi*tudinal studies* which will establish the relationship, if any between serum lipids in young, adult lif and the subsequent development of cerebrovascular disease.

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REFERENCES

1. Gertler M M Garn S. M and Lerman, J The inter-relationships of serum cholesterol, cholesterol esters nd phospholipids in health and coronary artery disease, Circulation 2:205 1950.
2. Oliver M F nd Boyd, G S. The plasma lipids and coronary artery disease, Brit Heart J 15:387 1953
3. Oliver M F and Boyd, G. S. Serum lipoprotein patterns in coronary sclerosis and associated conditions, Brit. Heart J 17:299 1955.
4. Mills, G. L and Wilkinson, P A. Plasma lipid levels and the diagnosis of coronary arteriosclerosis in England, Brit. Heart J 28:638, 1966.
5. Albrink, M J and M E B Serum triglycerides in coronary artery disease Arch. I t. Med. 103:4, 1959
6. Joint effort of the Technical Group of the Committee on Lipoproteins and Atherosclerosis and the Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council Evaluation of serum lipoprotein and cholesterol measurements as predictions of clinical complications of atherosclerosis, Circulation 14:691 1956.
7. A toma, A and Bersohn, I Serum triglyceride levels in South African Europeans and Bantu in ischaemic heart disease, Lancet 1:998 1960.
8. Ross Russell, R W Observations on intracerebral aneurysms, Brain 86:425 1963.
9. Cole, F M and Y tes, P O The occurrence and significance of intracerebral micro-aneurysms, J P th & Bact 93:393 1967
10. Dalsgaard-Nielsen, T Some clinical experience in the treatment of cerebral apoplexy (1 000 cases) Acta psychiat. Scandinav Suppl. 108 101 1956.
11. Heasman, M A., and Lipworth, L. Accuracy of certification of causes of death, General Register Office, Studies on Medical and Population Subjects N 20, H. M Stationery Office, 1966.

12. Prineas, J., and Marshall, J.: Hypertension and cerebral infarction, Brit. M. J. 1:14, 1966.
13. Cummings, J. N., Grundt, I. K., Holland, J. T., and Marshall, J.: Serum-lipids and cerebrovascular disease, Lancet 2:194, 1967.
14. Kannel, W. B.: An epidemiologic study of cerebrovascular disease. From cerebral vascular diseases, Transactions of the Fifth Conference held by the American Neurological Association and American Heart Association at Princeton, N. J., 1 January 1966, New York and London, 1966, Grune & Stratton, Inc., page 53.
15. Rifkind, B. M., Gale, M., and Jackson, I. D.: Serum lipid levels and body fat distribution in obese females, J. Clin. Path. 20:249, 1967.
16. Evans, J. G., and Ostrander, L. D.: Fasting serum triglycerides concentration and distribution of subcutaneous fat, Lancet 1:761, 1967.

Lidocaine in acute myocardial infarction

Experience in monitoring of patients with acute myocardial infarction in a coronary care unit (CCU) has shown that diverse arrhythmias occur sporadically during the initial *48 to 72 hours of illness.* Ventricular rhythm disorders are the *most frequent* with ectopic beats (VPB) observed in 70 per cent and ventricular tachycardia (VT) usually at a slow rate in 28 per cent of the patients. These arrhythmias generally do not compromise cardiac function nor are they perceived by the patient. However, they reflect an underlying electrical instability of the heart and *may* augur development of catastrophic derangement of the heart beat. Indeed, in a recent study, when minor arrhythmias were abolished, not a single episode of ventricular fibrillation resulted in 130 consecutive patients with acute myocardial infarction. The drug employed to control the minor ventricular rhythm abnormalities was lidocaine (1).

Lidocaine is a synthetic local anesthetic agent first employed by Southworth and associates[2] in 1950 for its antiarrhythmic properties. Its effectiveness in combating ventricular arrhythmias has been corroborated.[3-5] The clinical use of lidocaine has been reviewed in this JOURNAL. When given intravenously, an effect is observable within 15 to 30 seconds; this is due to rapid diffusion and cell membrane penetration. Within 20 minutes it is cleared from the circulation. The primary pathway of elimination is by hepatic degradation to free and conjugated phenols. Less than 10 per cent of this unaltered drug is found in the urine. Unlike procaine amide, lidocaine does not decrease arterial pressure nor reduce right ventricular contractile force. Its antiarrhythmic action is probably due to a reduction in Purkinje fiber automaticity.

Lidocaine is admirably suited for suppressing ventricular ectopic mechanisms in the patient with acute infarction. The ventricular arrhythmias develop unpredictably and need to be controlled promptly. Lidocaine can be administered intravenously in a single bolus with expectation of almost instantaneous effective action. Once the arrhythmia is abolished, a continuous intravenous infusion can be readily adjusted to a level just adequate for control. The *most serious* complication of myocardial infarction is hypotension leading to shock. Antiarrhythmic drugs such as quinidine and procaine amide impair cardiac contractility and reduce *peripheral resistance, thereby contributing to this* condition. Therapeutically adequate doses of lidocaine are less likely to compromise cardiac hemodynamics. Furthermore, lidocaine does not depress conduction, induce intraventricular or bundle branch block (BBB). In the critically ill patient with low cardiac output and reduced renal blood flow, the accumulation of antiarrhythmic drugs in the body deleteriously affects ventricular performance. Since lidocaine is eliminated by the liver, it can be employed even in the patient with oliguria. If untoward effects develop, cessation of infusion permits prompt assessment as to whether the drug is implicated. The transient action of lidocaine also allows frequent cessation of drug administration to determine whether antiarrhythmic measures are still required.

In the patient with acute myocardial *infarction,* treatment with lidocaine is indicated *for suppressing* VPB if they present any of the following: (1) occurrence early in the cycle with interruption of the T wave, especially if the Q-R'/Q-T is less than *0.85* where Q-R' represents the interval between the onset of QRS and VPB; (2) salvos of *two or more* successive ectopic beats; *(3) multiform configuration;* and (4) a *frequency* of VPB greater than 5 per minute. Lidocaine is given initially as an intravenous bolus of 25 to 50 mg. If ineffective it may be immediately followed with 100 mg. *If the VPB are abolished,* the drug is administered by continuous intravenous infusion in a concentration of 4 mg. per cubic centimeter at a rate of 1 to 4 mg. per minute. If ectopic mechanism recur increasingly, the rate of infusion may be inadequate, but once again the arrhythmias can be eliminated by an appropriate bolus injection and then recurrence can be prevented with a slightly higher infusion rate. Treatment is the same for paroxysmal VT.

Lidocaine was employed in *61 of 125* consecutive patients with myocardial infarction admitted to *CCU during the past year.* In 85 per cent it completely abolished ectopic activity. In 10 per cent ventricular mechanisms recurred and were controlled either by the addition of another antiarrhythmic

drug or by the technique of bolus injection as described above. In 2 per cent the arrhythmia was made worse by lidocaine. In this latter group, the basis for the ventricular ectopic activity was a slow ventricular rate, or what has been designated as arrhythmias of potential electrical instability.[1,8] In patients with this type of arrhythmia, acceleration of the ventricular rate by either atropine, isoproterenol, or pacemaker overdrive generally controlled the ectopic mechanisms. In 58 per cent of the patients, lidocaine was discontinued after 72 hours without recurrence of arrhythmia. In 10 per cent, however, this drug was required for 6 days or longer.

Serious untoward reactions were unusual. The elderly patient was more prone to central nervous system effects of the drug, especially when more than 2 mg. per minute was administered. Drowsiness, apprehension, disorientation, and stupor sometimes accompanied by twitching and fasciculation of facial muscles, was observed in less than 5 per cent of the patients. Exceptionally drowsiness and torpor persisted for as long as 24 hours after cessation of lidocaine. In one patient, convulsions developed which ceased immediately upon stopping the lidocaine infusion. In our experience lidocaine did not result in significant hypotension or respiratory depression. Impaired atrioventricular or intraventricular conduction or BBB did not occur.

The effective use of lidocaine in patients in a CCU suggests that the application of this therapeutic agent should be extended to an earlier phase of the coronary episode. The majority of coronary deaths are sudden and occur before the patient reaches a hospital. Indeed, when monitoring was instituted during ambulance transport to the hospital, the so-called flying squad, there was a high rate of ventricular fibrillation in this earliest phase of myocardial infarction.[10] Since the occurrence of catastrophic arrhythmias appears to be most common at the very inception of a coronary attack, this is the very time to institute prophylactic treatment. Lidocaine should, therefore, be one of the earliest measures employed as soon as the diagnosis is made. It is our view that 50 mg. of lidocaine should be given intravenously prior to transport of the patient to hospital. This should be carried out even if no ectopic beats are detected. A possible contraindication is the presence of bradycardia. There is no certainty that this approach will prove adequate; nevertheless, the low incidence of toxic reactions and the already accumulated evidence of effectiveness indicates the logic of such therapeutic intervention.

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REFERENCES

1. Lown, B., Fakhro, A., Hood, W. B., Jr., and Thorn, G. W.: The coronary care unit: new perspectives and directions, J.A.M.A. 199:188, 1967.
2. Southworth, J. L., McKusick, V. A., Pierce, E. C., and Rawson, F. L.: Ventricular fibrillation precipitated by cardiac catheterization. Complete recovery of a patient after forty-five minutes, J.A.M.A. 143:717, 1950.
3. Hitchcock, P., and Keown, K. D.: The management of cardiac arrhythmias during cardiac surgery, South. M. J. 52:702, 1959.
4. Likoff, W.: Cardiac arrhythmias complicating surgery, Am. J. Cardiol. 3:427, 1959.
5. Weiss, W. A.: Intravenous use of lidocaine for ventricular arrhythmias, Anesth. & Analg. 39:369, 1960.
6. Frieden, J.: Antiarrhythmic drugs. Part VII. Lidocaine as an antiarrhythmic agent, Am. Heart J. 70:713, 1965.
7. Harrison, C. D., Sprouse, J. H., and Morrow, G. A.: The antiarrhythmic properties of lidocaine and procaine amide: clinical and physiologic studies of their cardiovascular effects in man, Circulation 28:486, 1963.
8. Lown, B., Vassaux, C., Hood, W. B., Jr., Fakhro, A. M., Kaplinsky, E., and Roberge, G.: Unresolved problems in coronary care, Am. J. Cardiol. 20:494, 1967.
9. Kuller, L., Lilienfeld, A., and Fisher, R.: Epidemiological study of sudden death and unexpected deaths due to arteriosclerotic heart disease, Circulation 34:1056, 1966.
10. Pantridge, J. F., and Geddes, J. S.: A mobile intensive care unit in the management of myocardial infarction, Lancet 2:271, 1967.

Book reviews

BARORECEPTORS AND HYPERTENSION Edited by P Kezdi New York, 1967 Pergamon Press 460 pages. Price $16.00

This monograph of symposium held in Dayton Ohio on Nov 16 and 17 1965 is a good summary of important physiological phenomena of interest to linicians as well as physiologists. The par ticipants are outstanding and the subjects dis cussed extensive. For example the various ses sions included several papers on (1) physiology and control system theory of baroreceptors, (2) central control of baroreceptors for mecha nism, (3) baroreceptors control of effector organs, (4) anatomy and histology of the baroreceptors, (5) baroreceptors in hypertension and hypoten sion, nd (6) baroreceptors in clinical diagnosis and treatment. Each presentation is followed by interesting discussions. The reader will find this a very good book and will be particularly inter ested n the discussions. The book is highly recom mended

CONTROL OF THE PERIPHERAL CIRCULATION IN MAN By R. F Whelan, Ph D M D Springfield Ill 1967 Charles C Thomas Publisher 301 pages. Price $1 75

Professor Whelan has written an excellent mono graph on an important subject much neglected oday It is the peripheral circulation which is essential for good cellular health Yet, the less glamourous peripheral circulation receives little ttention Whelan has summarized important aspects of neurohumoral regulation of the pe ripheral circulation of man. He discusses such agents as angiotensin, serotonin, bradykinin histamine acetylcholine reserpine, alcohol, iso tine, epinephrine arterenol, isoproterenol, dop amine tyramine, and others. In addition reac tn and exercise hyperemia, nerve transmission, and vasodilator and vasoconstrictor nerves are discussed The text is clearly written the illus trations well selected and the bibliography is good The discussions, of course, are concerned with man and therefore the book should interest not only phy iologists and pharmacologists but linicians as well This book is highly recom mended as an excellent and authoritative presen tation of an important subject in medicine.

CARDIOPULMONARY BY LABORATORY BASIC METHODS AND CALCULATIONS. A Manual of Cardiopulmonary Technology By A Balfour Slonim M D Ph.D Bettye P Bell B.S and Sherryl E. Christensen, Springfield, Ill., 1967 Charles C Thomas, Publisher 263 pages. Price $15 3

This monograph is a manual which describes the various basic methods, procedures and evalua tions in current use t measure cardiac and pulmo nary function. Brief physiological principles of functional changes are also presented. Those in active experimental and service laboratories will find little use of such a manual whereas those planning a laboratory or interested in learning the method and calculations will find this a good source of important information. The authors have rendered a fine service t the cardiopulmo nary field. The discussions are brief and clear tables and formulas are numerous, and the se lected bibliography good. Obviously investi gators launching research programs must employ methods most useful for their own studies which, therefore, may require other special procedures or modifications They nevertheless, will also find this manual good reference.

ASSISTIERTE ZIRKULATION Mechanical assistance of the circulation Prof Dr F Loogen Dr B. Bostroem Dr U Gleichmann, and Doz. Dr H Kreuzer Dusseldorf Germany Stuttgart 1967 Georg Thieme Verlag 170 pages.

These proceedings of a meeting held during June 15 through 17 1967 at Bad Nauheim summarizes ery well the studies at present Among the 16 subject discussed were mechanism of assisting the circulation, counterpulsation enoarterial phased pulsatile partial bypass, left heart by pass, mechanical support of the failing heart, hemodynamic effects and concepts assisted circulation, and the artificial heart The papers are well written and nicely illustrated th n ppended bibliography Discussions re also included It is evident t the critical reader that assisting the circulation is highly experimental. The clinical value to the patient with heart dis ease of assisting the circulation still await evi dence Nevertheless, this is a good summary of present day work nd thinking

VENTILATION UND ATEMMECHANIK BEI SÄUGLINGEN UND KLEINKINDERN UNTER NARKOSEBEDINGUNGEN. By J W wersik, Berlin Heidelberg, New York, 1967 Springer Verlag 84 illustrations, 151 pages. Price $8 00

In view of the lack of reliable information about the physiology of pulmonary ventilation in infants, there is discrepancy of opinion about the suitability of various types of equipment for anesthesia in infants in respect to dead space and resistance. The author has attempted t fill this gap by extensive and detailed investig tions. In substantial number of children from the first day t 6 years of age the frequency tidal volume, and minute volume of pulmonary ven tilation were measured during various types of anesthesia and in addition maximum inspira tory nd expiratory force ere determined. For

children over 3 years of age, equipment designed for adults can be used but modifications are needed for infants in order to prevent hypoventilation.

The work of respiration in spontaneous, undisturbed breathing was determined by means of measurement of esophageal pressure and pneumotachograms. On the basis of these results, 2 nomograms were constructed for determination of the mechanical work of breathing from the volume of pulmonary ventilation and esophageal pressure amplitude. Under normal conditions, the energy cost of breathing is usually about 2 per cent of total oxygen consumption, but there is a large variation due to changes of the efficiency of respiratory muscles. Additional respiratory work against resistance of anesthesia equipment ranged between 0.01 mkp per minute in infants (3 kilograms of body weight) to 0.09 mkp per minute in children 6 years of age (23 kilograms of body weight). Resistance due to endotracheal tubes may double the respiratory work but there is good reason to assume that this increase is still within the work capacity of respiratory muscles.

While the book is mainly written for anesthesiologists, the fundamental information about mechanics and energetics of breathing is valuable for the pediatric cardiologist.

DIGITALIS THERAPY. A REAPPRAISAL OF DIGITALIS AND CARDIAC GLYCOSIDES. By Alan F. Lyon, M.D. and Arthur C. DeGraff, M.D. Saint Louis, 1967. The C. V. Mosby Company. 38 pages. Price $[illegible].00.

This booklet contains 10 short, concise, well-written and important aspects of digitalis and its use which appeared in the AMERICAN HEART JOURNAL recently. Among the 10 subjects discussed are digitalis action at the cellular level, hemodynamic effects of the cardiac glycosides, indications, dosage and toxicity digitalis, and its management. This is a very fine review of the subject which should prove extremely valuable to the busy physician.

Books received

BIOCHEMISTRY OF GLYCOPROTEINS AND RELATED SUBSTANCES. Cystic Fibrosis—Part II. Edited by E. Rossi and E. Stoll, coordinated by S. Rosemann. (Proceedings of the 4th International Conference on cystic fibrosis of the pancreas (mucoviscidosis) Geigy Symposium, Berne/Grindelwald, September 1966.) Basel, 1968, S. Karger. 322 pages. Price $19.60.

HERZ- UND GEFÄSSKRANKHEITEN. By H. Klepzig. Stuttgart, 1968. Georg Thieme Verlag. 284 pages. Price $2.45.

KILLER SMOG. By William Wise. Chicago, 1968. Rand McNally & Co. 161 pages. Price $5.95.

Announcements

A Graduate Course in Medical Hypnosis is being offered to physicians and dentists by the University of Pennsylvania Graduate Division, School of Medicine. There will be 20 four-hour afternoon sessions for a total of 80 hours beginning Sept. 26 1968. The course will be given at the Institute of the Pennsylvania Hospital, 111 N 49th St., Philadelphia, Pa. 19139 For further information, write to Office of the Director Division of Graduate Medicine, 237 Medical Laboratories, University of Pennsylvania, Philadelphia, Pa. 19104.

A Five Day Congress in Cardiology will be held in Mexico, Oct. 29 through Nov 2, 1968, the week after the Olympic Games. The faculty will be composed of *Abdo Bisteni, M D* Mexico P G F Nixon, M.R.C.P London Joseph K. Perloff M D Washington and Jose Ponce de Leon, M D Mexico. The directors will be Demetrio Sodi-Pallares, M D Mexico, and Henry J L Marriott, St. Petersburg For further details, write to the Rogers Heart Foundation, 500 First Federal Building St. Petersburg Fla.

The Second International Symposium on Atherosclerosis will be held at The Conrad Hilton Hotel, Chicago, Ill., on Nov 2 5 1968. For further information, write to Louis N Katz, M D General Chairman, Chicago Heart Association 22 West Madison St., Chicago, Ill. 60602.

A Two-Day Meeting on Medical and Surgical Problems in Workmen's Compensation will be held by the American Academy of Compensation Medicine Nov 7 and 8 1968 at the New York University Medical Center New York, N Y There will be no registration fee, but physicians interested in attending are urged to write to the Academy so that appropriate arrangements can be made for the meeting The address of the American Academy of Compensation Medicine is Box 180 Radio City Station, New York, N Y 10019

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Editorial

The long term results of closure of ventricular septal defect with pulmonary vascular disease

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The association of pulmonary vascular disease with ventricular septal defect is known to carry a poor prognosis.[1-4] We should therefore like to know whether we can expect such a patient to live a longer and more useful life after surgical closure of the defect, whether the operative risk is acceptable, and whether age, severity of the pulmonary vascular disease, or any other factor affects the prognosis.

It has been only 13 years since the first reports of successful closure of ventricular septal defects,[5] so that, bearing in mind the high early operative mortality rate in patients with pulmonary vascular disease and a reluctance to recommend surgical closure, there can be relatively few survivors who could as yet have outlived their medical prognosis. Assessment of the long term postoperative results must therefore be based on the necessarily limited data available thus far.

Diagnosis and assessment of pulmonary vascular disease. Evaluation of postoperative results is made difficult by the lack of general agreement on the definition of pulmonary vascular disease and the criteria for the assessment of its severity. The diagnosis is essentially a histological one, and the changes in the pulmonary vasculature have been well documented and graded in terms of severity.[7] However, a single lung biopsy specimen may be misleading and is not generally accepted as a routine investigation. Since there is no other single diagnostic criterion, we must rely on hemodynamic, electrocardiographic, and radiographic data, aware that evaluation is open to error in calculation and individual obscure interpretation. Hemodynamic data, reflecting events at a particular moment of time and circumstance, are particularly prone to misinterpretation.

The clinical picture of ventricular septal defect with severe pulmonary vascular disease is well known. Its development may be suspected by increasing clinical, radiographic, and electrocardiographic evidence of right ventricular hypertrophy, a loud pulmonary second sound, systolic click, absence of thrill, and an ejection systolic murmur. Evidence of an appreciable left-to-right shunt—left ventricular hypertrophy and apical third heart sound and mid-diastolic murmur—would still be expected.

Acceptable hemodynamic evidence of pulmonary vascular disease in the resting and lightly sedated individual would be a

pulmonary vascular resistance of above 5 units or 400 dynes/sec./cm $^{-5}$ (in children of 4 years of age and upward) a pulmonary to systemic flow ratio of 2 1 or less and a pulmonary to systemic resistance ratio of 0 25 or above. This index forms one of the most useful indices of severity ratios of 0.25 to 0 45 0 45 to 0 75 and 0 75 and above indicating mild moderate, or severe pulmonary vascular disease, respectively [9] This grading has been used subsequently where possible. A pulmonary artery pressure at or near systemic levels is to be expected in patients with pulmonary vascular disease, but is obligatory with any large ventricular septal defect and thus, the equating of pulmonary artery pressure with pulmonary vascular disease is misleading The pulmonary vascular resistance is usually only fixed in severe pulmonary vascular disease and can often be lowered by pulmonary vasodilators.[9] Hypoxia [11] and disturbances of acid base balance[11] may induce pulmonary vasoconstriction particularly in infants and small children thus increasing the resistance and giving a false impression of the severity of the pulmonary vascular disease

Results of surgical closure There are approximately 135 patients reported in the literature[1,14,22,26] with a presumptive diagnosis of pulmonary vascular disease who have been followed up and restudied after closure of their ventricular septal defect. The maximum follow up period is 8 years.

The majority of patients have become asymptomatic[9,24] and are able to lead unrestricted lives. Most of the children show a return toward their expected rate of growth [9,24] and may ultimately acquire good physique A gradual return toward normal chest shape has also been noted [1] The over-all heart size and that of the main pulmonary artery diminishes, though some cardiomegaly may persist.[10,24] Complete right bundle branch block is a common postoperative finding its association with postoperative left axis deviation is uncommon[19] but could potentiate the development of complete atrioventricular block.[24]

Immediately after closure of a ventricular septal defect with Grades 1 to 3 histological changes,[3] and sometimes with Grade 4 changes, there is a fall in pulmonary artery pressure and in the ratio of pulmonary to systemic arterial pressures, the decrease being related to the severity of the pulmonary vascular disease.[22] Failure of the pulmonary artery pressure to fall probably indicates severe pulmonary vascular disease, impaired right ventricular function or a combination of both. A fall in pulmonary artery pressure was recorded immediately after closure of the defect in 28 children with pulmonary vascular disease but a dominant left to-right shunt and reinvestigation of 25 of them one or more years postoperatively showed pulmonary artery pressures approximating to those immediately after closure. In one-third of the children, the pulmonary artery pressure and ratio of systemic to arterial pressures had returned to normal values. [9]

While a fall in pulmonary artery pressure occurs in the great majority of patients,[9,10,22,26] it could of course be attributed to the elimination of the left to-right shunt following closure of the ventricular septal defect and except possibly in patients *when a serial fall has been reported* [1,4] cannot be used as evidence of regression of pulmonary vascular disease. At present, there is no direct evidence of a fall in pulmonary vascular resistance immediately following closure of a ventricular septal defect and none was recorded in 16 patients with moderate or severe pulmonary vascular disease in whom it was estimated [22] There are conflicting findings on the pulmonary vascular resistance in patients reinvestigated post operatively Some investigators have found no evidence of a fall in the resistance [13,14,15,16] but more encouraging *results have been* reported from centers where the patients were predominantly children and the series comparatively large.[9,10,1 ,26] Considering the total number of reported patients reinvestigated the pulmonary vascular resistance had fallen in over a half Of 25 children reinvestigated up to 6 years after closure of their ventricular septal defect 85 per cent showed a fall in the ratio of pulmonary to systemic resistance and this ratio fell to 0.25 or less in over a quarter of them. [9] In another series of 40 patients there was a significant fall of pulmonary

to systemic resistance of 25 per cent or more in 58 per cent of the patients with moderate and 50 per cent with severe pulmonary vascular disease.[36] Improvement to normal or near normal values of pulmonary vascular resistance and resistance ratios may occur even in patients assessed as having severe pulmonary vascular disease,[19, 36] although it has been suggested that some of these patients may have had a falsely high assessment of severity based on misleading hemodynamic data.[19]

There is some evidence that the pulmonary vascular resistance may continue to fall long term. A progressive fall was reported in 5 out of 6 children serially recatheterized up to 8 years after closure of their defect.[4] This was the finding in only one out of another 11 children similarly restudied over the same period of time but 4 of these already had normal pulmonary vascular resistance at their first postoperative catheter[19] the other 6 showed no significant change. In an unpredictable minority of patients, forming 16 per cent of one series[36] the pulmonary vascular resistance continued to rise after closure of the defect.

Although we may suspect that the fall in pulmonary vascular resistance shown by the majority of patients signifies regression of pulmonary vascular disease we lack information on the relative roles of pulmonary vasodilatation and histological regression. Regression of medial and early intimal changes have been shown to occur in patients with ventricular septal defect who have had pulmonary artery banding[31] but we still lack evidence of the long term regression of the more advanced changes. There is some evidence[1, 36] that the post operative prognosis is more favorable for small children who may better reverse the changes or compensate for them. Even in those patients in whom there is no demonstrable postoperative change in the severity of the pulmonary vascular disease the abolition of the left-to-right shunt, and any fall in pulmonary artery pressure and possibly in left atrial pressure may be factors mitigating against its progression, thus improving the long term prognosis. A significant residual left-to-right shunt may affect this disadvantageously but a very small residual defect does not appear to do so. The majority of patients have good evidence of residual pulmonary vascular disease, confirmed by respiratory function tests showing evidence of restrictive lung disease with increased physiological dead space and reduced diffusing capacity.[11] Also while they may achieve a satisfactory rise in cardiac output and fall in pulmonary vascular resistance on mild effort, on more vigorous exercise the pulmonary vascular resistance may rise, tachycardia and severe pulmonary hypertension develop and arterial oxygen saturation and stroke output fall.[4] It seems probable that even those patients with normal resting hemodynamics may show an abnormal response to exercise.

Operative mortality. The immediate over all operative mortality rate for patients (excluding infants) with ventricular septal defect and pulmonary vascular disease has improved over recent years and may now lie between 9 and 15 per cent.[1, 2, 36] These figures include patients with multiple ventricular septal defects, associated ostium secundum defects, small patent ductus arteriosus and trivial valvular abnormalities. In patients where resistance ratio approaches 1 the mortality rate increases, however, the over-all improved results are attributable to conservation of right ventricular function by suitable ventriculotomy or transatrial approach, avoidance of complete heart block, and improved immediate postoperative care. Surgical closure of ventricular septal defects in infancy has hitherto carried a high mortality rate whether or not there is associated pulmonary vascular disease. However an improved mortality rate has recently been reported[38] and further improvement may be expected both in this age group and in the older children.

Late deaths have been reported. Patients with progressive pulmonary vascular disease despite closure of their defect, have died in congestive cardiac failure and sudden deaths have been reported in patients with evidence of residual pulmonary vascular disease[36] presumably due to a sudden increase in pulmonary vascular resistance and fall in cardiac output.

Selection of patients. It is doubtful whether any benefit can be expected by closing the ventricular septal defect in the presence of

a dominant right-to-left shunt and low pulmonary blood flow and the operative mortality rate is high. Although it has been suggested that the level of pulmonary vascular resistance should be a major operative criterion,[18] the ratio of pulmonary to systemic resistance would seem to be a more useful index. With a ratio approaching 1, it is particularly important to assess all available data before advising closure of the defect. An acceptable mortality rate and the hope of long-term benefit can only be achieved if a dominant left-to-right shunt can be clearly shown not only hemodynamically but by clinical, electrocardiographic, and radiological evidence; disappearance of the apical diastolic flow murmur removes a very useful criterion of a good operative candidate.

Conclusion

The long-term results of closure of ventricular septal defect associated with pulmonary vascular disease awaits the passage of time. Present indications are that though the patients are left with residual pulmonary vascular disease, the prognosis for many of them may be improved; the immediate operative mortality rate is now an acceptable one except in infancy, provided there is good evidence of a dominant left-to-right shunt. Additional information on the correlation of pathological with hemodynamic and clinical findings would be a helpful contribution toward further knowledge of operative criteria and postoperative prognosis.

Reports of late sudden deaths, abnormal respiratory function tests, and impaired exercise performance and known residual pulmonary hypertension suggest that the long-term prognosis could be further improved if respiratory tract infections were treated promptly, high altitudes avoided, and athletic activities restricted.

The long-term prognosis favors those with mild pulmonary vascular disease and young children and it is known that pulmonary vascular disease may be rapidly progressive.[24] Thus, there is a good argument for advising closure of the defect in infants in whom there is evidence that pulmonary vascular disease is developing just as soon as an acceptable surgical mortality rate can be offered. If the operative risk in small babies can be reduced to that of older children, the indications for closure of ventricular septal defects must again be reviewed. It is conceivable that a policy of closing all high-pressure, low-resistance ventricular septal defects in infancy may eventually be adopted, thereby hopefully greatly lessening the incidence of the serious complication of pulmonary vascular disease.

REFERENCES

1. Brotmacher, L., and Campbell, M.: The natural history of ventricular septal defect, Brit. Heart J. 20:97, 1958.
2. Wood, P.: The Eisenmenger syndrome, Brit. M. J. 701:755, 1958.
3. Selzer, A., and Laqueur, G. L.: The Eisenmenger complex and its relation to the uncomplicated defect of the ventricular septum. Review of thirty-five autopsied cases of Eisenmenger complex, including two new cases, Arch. Int. Med. 87:218, 1951.
4. Bloomfield, D. K.: The natural history of ventricular septal defect in patients surviving infancy, Circulation 29:914, 1964.
5. Kirklin, J. W., DuShane, J. W., Patrick, R. T., Donald, D. E., Hetzel, P. S., Harshbarger, H. G., and Wood, E. H.: Intracardiac surgery with the aid of a mechanical pump-oxygenator system (Gibbon type). Report of eight cases, Proc. Staff Meet. Mayo Clin. 30:201, 1955.
6. Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. L.: Direct vision intracardiac correction of congenital anomalies by controlled cross circulation: results in 32 patients with ventricular septal defects, tetralogy of Fallot, and atrioventricularis communis defects, Surgery 38:11, 1955.
7. Heath, D., and Edwards, J. E.: A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac defects, Circulation 18:533, 1958.
8. Kirklin, J.: Ventricular septal defect with pulmonary vascular disease, New Zealand Med. J. Cardiac Suppl. 64:34, 1965.
9. Blount, S. G., Jr., and Woodwark, G. M.: Considerations involved in the selection for surgery of patients with ventricular septal defects, Am. J. Cardiol. 5:223, 1960.
10. Hallidie-Smith, K. A., Hollman, A., Cleland, W. P. C., Bentall, H., and Goodwin, J. F.: The effect of surgical closure of ventricular septal defect upon pulmonary vascular disease, Circulation. In press.
11. Rudolph, A. M.: Biochemical and haemodynamic aspects of cyanosis. The heart and circulation in newborn infants, New York, 1966, Grune & Stratton, Inc., page 173.
12. Burchell, H. B.: Regression of pulmonary vascular hypertension after care of intracardiac defects. Pulmonary circulation. An international symposium, New York, 1959, Grune & Stratton, Inc., page 215.

13 Lucas, R. V J Adams, P J Anderson, R. C., Meyne, N G., Lillehei, C. W and Varco, R L. Natural history of isolated ventricular septal defect A serial physiologic study Circulation 24 1372, 1961.

14 Leachman, R. D., Observations on the pulmonary vascular resistance following surgical closure of high resistance ventricular septal defects, Cardiovas. Res. Center Bull. 2:23 1963.

15. Hallman, G. L., Cooley D A., Wolfe, R. R., and McNamara, D G. Surgical treatment of ventricular septal defect associated with pulmonary hypertension J Thoracic & Cardiovas. Surg 48:588, 1964.

16. Lillehei, C. W Levy M J Adams, P and Anderson, R. C. High pressure ventricular septal defects, J.A.M A. 188:949 1964.

17 Ross, J Morrow A. G., and Braunwald, E. Regression of severe pulmonary hypertension after repair of defect of the ventricular septum in patient with bidirectional shunt, New England J Med. 270:946, 1964

18. Reeve, R., Selzer A Popper R. W Leeds, R. F and Gerbode, F Reversibility of pulmonary hypertension following cardiac surgery Circulation (Suppl 1) I 107 1966.

19 Kimball, K. G., and McIlroy M B Pulmonary hypertension in patients with congenital heart disease, Am. J Med. 41:883, 1966.

20. Cartmill, T B DuShane, J W McGoon, D C., and Kirklin, J W Results of repair of ventricular septal defect, J Thoracic & Cardiovas Surg 52:490, 1966.

21 Heath, D Helmholz, H F J Burchell, H. B., DuShane, J W Kirklin, J W and Edwards, J Relation between structural changes in the small pulmonary arteries and immediate reversibility of pulmonary hypertension following closure of ventricular and atrial septal defects, Circulation 18 1167 1958.

22. Theye, R. A., and Kirklin, J W Physiologic studies following surgical correction of ventricular septal defect, Circulation 27:590 1963

23 Damman, J F McEachen J A., Thompson, W M., Smith, N S., and Muller W H. The regression of pulmonary vascular disease after the creation of pulmonary stenosis, J Thoracic Surg 42 722, 1961

24. Kolbertus, H., Cowan, J and Halfidie Smith K. A. Conduction disturbances before and after surgical closure of ventricular septal defect, Brit. Heart J In press.

25 Sigmann, J M Stern, A M and Sloan, H. E. Early surgical correction of large ventricular septal defects, Pediatrics 39:4, 1967

26. Anderson, R A., Levy A. M Naye, R. L., and Tabakin, B. S Rapidly progressing pulmonary vascular obstructive disease. Association with ventricular septal defects in early childhood, Am J Cardiol. 19:854 1967

Sensitivity and specificity of electrocardiographic evaluation of LVH in 364 unselected autopsy cases

A criterion, $R_{V6} \geq 18$ mm., is proposed

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The currently used electrocardiographic criteria for left ventricular hypertrophy (LVH) are for the most part, inadequate.[1-4] The search for an accurate electrocardiographic criterion for the diagnosis of LVH is constantly being pursued.[5] The electrocardiographic criteria are empirical and are based on several assumptions (1) a greater electromotive force[6] is generated by the hypertrophic left ventricle causing tall R waves in Leads I aVL and V_{5-6} with deep S in V_{1-2} (2) a longer period is required for the activation wave[4] to travel from the endocardium to the epicardial surface of the entire ventricle, causing prolonged intrinsicoid deflection and QRS duration or (3) a change in the direction of repolarization[1,3,4] causes ST depression and inverted T waves as well as prolonged Q-T interval. The use of ST T segment and T waves and Q-T interval changes as criteria has been discouraged[1,4,18] because of the alteration of these values by digitalis, quinidine ischemic heart disease electrolyte imbalance hyperventilation and myocarditis.

The current study was initiated by the rather discouraging inadequacy of voltage criteria and the intrinsicoid deflection in making an electrocardiographic diagnosis of LVH in older patients when the criteria used were compared with the heart specimen at autopsy Furthermore, the majority of investigative studies utilizing voltage criteria for the diagnosis of LVH lack the evaluation of sensitivity specificity or predictive value of their specific criteria. It is our intention to present a voltage criterion (R_{V6} equal to or greater than 18 mm.) which may be used along with other voltage criteria for a better evaluation of LVH and to compare this criterion with the more commonly used voltage criteria as to their specificity sensitivity and predictive values.

Materials and method

All adult patients who had electrocardiograms (ECG's) taken within one year before their deaths from 1961 to 1964 at Harbor General Hospital and who also had postmortem examinations were reviewed there were 364 such patients. According to the pathological criteria of LVH subsequently described 163 patients

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had LVH, 145 patients did not have LVH, and 56 patients were considered as borderline or intermediate group.

Of these 163 patients classified as having LVH, 63 had pure LVH, 42 had biventricular hypertrophy, 47 had LVH with myocardial infarction, and 11 had biventricular hypertrophy with myocardial infarction. Excluding left and right bundle branch blocks (BBB's), there were 60, 39, 37, and 9 patients in the respective LVH groups available for pathological and electrocardiographic analysis.

The pathological criterion used for LVH was a heart weight of 420 grams or more and thickness of the left ventricle of over 14 mm. The pathological criterion used for right ventricular hypertrophy (RVH) was thickness of the right ventricle equal to or greater than 5 mm., or over 3 mm. with an obvious dilated right ventricle. The pathological criterion used for myocardial infarction was gross fibrosis of the myocardium or an area of obvious fresh myocardial infarction. In this study, minimal microscopic fibrosis of the myocardium was excluded as evidence for myocardial infarction. The pathological criterion used for the control group was a heart weight below 370 grams and thickness of the left ventricle of less than 14 mm. The intermediate group consisted of patients with a heart weight between 370 and 420 grams regardless of the thickness of the left ventricle. The gross heart weight included approximately 20 to 60 grams of attached valves and short remnants of the great vessels. The left ventricular wall thickness of 14 mm. was used in order to minimize possible error in overestimation of the actual wall thickness because of improper cutting and inclusion of papillary muscle attachment. Our investigation was essentially nonselective and not based on the clinical blood pressure as a criterion for LVH. Of the 56 patients in the intermediate group, 15 had a systolic pressure of over 170 mm. Hg or a diastolic pressure of over 95 mm. Hg, but were not classified as having LVH. This borderline group also includes 23 patients with a heart weight of less than 420 grams but with a ventricular wall thickness of 14 mm. or more.

The mean age of the 163 patients with LVH was 69.8 years (Table I); of the 145

Table I. Mean age, sex, heart weight, and ventricular thickness of the LVH, control, and intermediate groups

Groups	Mean age (yr.)	No. of patients	Sex: M	Sex: F	Mean heart weight (Gm.)	Thickness: LV (mm.)	Thickness: RV Normal (mm.)	Thickness: RV Hypertrophy (mm.)
Group A								
LVH only	67.6	63	46	17	502	16.0	3.4	—
LVH + RVH	70.0	42	29	13	572	16.7	—	5.7
LVH + MI	72.3	47	32	15	518	16.9	3.8	—
L, RVH + MI	73.4	11	5	6	546	18.3	—	6.0
Entire group with LVH	69.8	163	112	51	525	16.6	3.57	5.76
Group B								
Control group	66.2	145	61	84	305	12.9	3.4	—
Group C								
Intermediate group	68.9	56	32	4	384	14.9	3.8	—
Groups B and C =	67.2	201	93	108	329	13.3	3.5	—

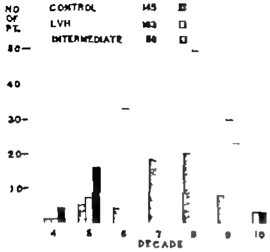

Fig. 1. Age distribution of 364 autopsy cases by decades.

normal subjects 66.2 years, and of the 56 patients in intermediate group 68.9 years. The age distribution in decades is shown in Fig. 1.

All questionable ECG's were reviewed by two or more observers. A total of 18 patients with BBB or intraventricular conduction defect were excluded from the study as previously stated. The voltage and intrinsicoid deflection electrocardiographic criteria for LVH used in this study follow: (1) $(R_1 + S_3) - (S_1 + R_3) \geq$ 18 mm; (2) $R + S_3 \geq$ 25 mm; (3) R in $aV_L \geq$ 11 mm;[10,11] (4) R in $aV_L \geq$ 8 mm;[12] (5) intrinsicoid deflection $\geq$ 0.05 sec.; (6) $S_V + R_{V5-6} \geq$ 35 mm or R $_5$ or V $\geq$ 25 mm;[12] of (7) our proposed criterion of R $\geq$ 18 mm.

All patients had ECG's taken with the standard limb leads, augmented unipolar limb leads, and standard unipolar chest leads. The standardization used was 10 mm. of deflection for every 1 mv. of input. Upward deflections were measured from the top of the baseline to the peak of the upstroke; downward deflections were measured from the bottom of the baseline to the peak of the downstroke. The intrinsicoid deflection was measured from the *beginning* of the QRS to the top of the R in V_5 or V_6.

The results were analyzed by evaluation of sensitivity, specificity, predictive value of a positive test, and predictive value of a negative test for a specific criterion used.[13]

The sensitivity of a criterion for LVH is defined as the ability of a criterion to give a *positive* finding when the person tested truly has LVH confirmed by autopsy.

$$\text{Sensitivity} = \frac{\text{No. of persons with positive ECG criterion}}{\text{All patients with confirmed LVH tested}} \times 100$$

The specificity of a criterion for LVH is defined as the ability of a criterion to give a *negative* finding when the person tested does not have LVH.

$$\text{Specificity} = \frac{\text{No. of control persons negative to the criterion}}{\text{All control persons tested}} \times 100$$

The predictive value of a positive test is the percentage of times that a *positive* finding of a criterion for LVH will detect a person with confirmed LVH.

$$\text{Predictive value of positive test} = \frac{\text{No. of persons with confirmed LVH and positive criterion}}{\text{All persons with positive LVH criterion (true and false positive)}} \times 100$$

The predictive value of a negative test is the percentage of times that a *negative* finding of a criterion for LVH will detect a person without LVH.

$$\text{Predictive value of negative test} = \frac{\text{No. of control patients with negative criterion}}{\text{All persons with negative LVH criterion (false and true negative)}} \times 100$$

Results

The total number of autopsies from 1961 to 1964 at Harbor General Hospital was 2,084; 364 of the adult autopsied cases had had recent ECG's. The occurrence of LVH in 163 of these 364 patients appeared astonishingly high. This incidence cannot be viewed as the incidence of LVH in the same age group in a general population. Because this incidence did not represent the hospital population that did not come to autopsy, the 364 autopsy patients were selected because they had had recent ECG's prior to death and only in this way is this group essentially selective.

As shown in Table I, LVH was more common in men, with a male-to-female

Table II. Comparison of heart weight to body height, weight, and surface area in the control, LVH, and intermediate groups

Groups	Sex	No. of patients	Heart wt. (Gm.)	Body wt. (Kg.)	Bod. ht. (cm.)	Bod. surface area (M^2)	Ratio of ht. wt. (Gm.) to: Body surface (M^2)	Body wt. (Kg.)	Bod. ht. (cm.)
LVH only	M	46	510.0	75.2	167.2	1.84	277	67.8	3.05
	F	17	483.5	72.7	159.8	1.75	276	66.5	3.02
LVH + RVH	M	29	570.3	74.3	170.3	1.84	310	76.7	3.35
	F	13	576.9	74.2	159.4	1.72	325	77.7	3.62
LVH + MI	M	32	507.0	74.4	165.5	1.83	278	68.1	3.06
	F	15	538.0	60.3	156.3	1.63	331	89.2	3.44
LVH, RVH + MI	M	5	526.0	55.4	159.0	1.56	338	94.9	3.31
	F	6	562.0	70.9	161.8	1.75	321	79.3	3.47
Total	M	112	521.0	73.8	167.2	1.82	288	70.6	3.12
	F	51	534.0	69.2	158.9	1.71	310	77.2	3.36
Control	M	61	308.0	61.7	163.7	1.65	187	50.0	1.88
	F	84	304.0	55.9	149.0	1.53	198	54.3	2.04
Intermediate group	M	32	383.3	69.8	168.3	1.77	216	54.9	2.27
	F	24	384.8	67.3	155.3	1.65	231	57.1	2.48

LVH, Left ventricular hypertrophy; RVH, right ventricular hypertrophy; MI, myocardial infarction.

ratio of 2.2 to 1. In the intermediate group the male-to-female ratio was 1.3 to 1; in the normal group it was 0.85 to 1.

The mean heart weight of the 163 patients with LVH was 525 grams, of the 145 patients in the control group it was 305 grams, and of 56 patients in the intermediate group it was 384 grams (Table I). The mean heart weight of the LVH group was 220 grams greater than that of the control group. The mean thickness of the left ventricle in the LVH group was 16.6 mm.; it was 12.9 in the control group. The mean thickness of the right ventricle in the LVH group without RVH was 3.57 mm.; it was 3.4 mm. in the control group. It was 5.76 mm. in the LVH group with RVH.

As shown in Table II, the mean body weight of the entire LVH group was 12 to 13 kilograms more than that of the control group. Therefore, to be of comparative significance, the ratios of the heart weight to body weight, to body height, and to body surface were evaluated. These respective ratios were 41, 65, and 55 per cent higher in the entire LVH group as compared with those of the control group, regardless of sex. As one would expect, the patients with biventricular hypertrophy had greater heart weights than the patients with LVH only.

The sensitivity of any individual voltage criterion or intrinsicoid deflection for the diagnosis of pure LVH (Table III) was of Noth and associates. However, the criterion of Sokolow and Lyon[12] and the authors' proposed criterion of $R_V > 18$ mm. Of the 60 patients with pure LVH, 19 or 32 per cent can be diagnosed by a combination of the criteria from A to F. An increase in sensitivity to 43 per cent, or 26 of the 60 patients, was obtained when the authors' criterion was also included. Similarly, in the three other groups of the entire LVH group, the authors' criterion increased the sensitivity by 5 to 12 per cent, with a mean increase of 9 per cent in the entire LVH group.

Table III *Sensitivity of various LVH criteria*

Criteria	Left ventricular hypertrophy 145 pts.										Control, 145 pts.		Intermediate, 56 pts.	
	Pure LVH 60 pts.		LVH + RVH 39 pts.		LVH + MI 37 pts.		LVH RVH + MI 9 pts.		Total 145 pts.		False positive		(?) False positive	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A. Lewis[7] $(R_1 + S_3) - (S_1 + R_3) \geq 18$	5	8.3	6	15.4	8	22.0	0	0	19	13.0	6	4.1	6	10.6
B. Gubner and Ungerleider[8] $(R_1 + S_3) \geq 25$	3	5.0	3	7.7	3	8.0	0	0	9	6.2	2	1.4	3	5.3
C. Goldberger[10] and Katz[9] $V_1 \geq 11$	5	8.3	4	10.2	3	8.0	0	0	12	8.2	4	2.8	3	5.3
D. Mazzoleni and associates[12] $V_L \geq 8$	11	18.0	6	15.4	8	22.0	3	33.3	28	19.1	12	8.3	9	16.0
E. Noth and co-workers[14] Intrinsicoid deflection $\geq$ 0.05	6	10.0	6	15.4	6	16.0	2	22.2	20	13.7	2	1.4	2	3.6
F. Sokolow and Lyon[15] $S_{V1} + R_{V5,6} \geq 35$ or	12	20.0	8	20.5	5	13.5	3	33.3	28	19.1	8	5.6	9	16.0
R_{V5} or $V \geq 25$	9	15.0	3	7.7	2	5.4	2	22.2	16	11.0	6	4.1	2	3.6
G. Authors $R_{aVL} \geq 15$	13	22.0	11	28.2	8	22.0	4	44.4	36	24.6	10	7.0	4	7.1
A to F	19	32.0	17	43.7	14	38.0	5	55.0	55	37.6	13	9.0	19	34.0
A to G	26	43.0	20	51.3	16	43.0	6	67.0	68	46.9	15	10.4	19	34.0

Our study indicates that the presence of myocardial infarction or RVH does not significantly impair the sensitivity of criterion used. In fact, in most instances, except that of Sokolow and Lyon[15] the sensitivity either remains the same or increases slightly in contrast to the report of Lipsett and Zinn[17] Most investigators exclude from their series cases of LVH complicated with myocardial infarction or RVH

The lowest percentage of false-positive results (Table IV) was attained by the criteria of Gubner and Ungerleider[8] and of Noth and associates.[7] However the criterion of Gubner and Ungerleider[8] also had the lowest sensitivity The criterion with the highest percentage of false-positive results was that of Mazzoleni and associates.[12] Our proposed criterion had a relatively high percentage of false-positive results, and increased them by 1.4 per cent when it was used in combination with the other criteria. However an increase in sensitivity of 8.9 per cent was achieved at the expense of a 1.4 per cent increase in false-positive results.

Table IV tabulates the sensitivity specificity and predictive value of a positive or negative finding for the criteria studied Many investigators in their studies of electrocardiographic criteria for LVH omitted evaluation of sensitivity and specificity Obviously a highly sensitive criterion with a low specificity is not ...able and a highly specific criterion ... low sensitivity is equally undesirable. ... predictive value of a criterion is

Table IV Sensitivity specificity and predictive values of electrocardiographic LVH criteria

Criteria	*LVH*	*Control*	*Sensitivity (per cent)*	*Specificity (per cent)*	*Predictive value positive (per cent)*	*Predictive value negative (per cent)*
A. Lewis $(R + S_3) - (S_1 + R_3) > 18$	19	6	13 0	95 7	71 1	52 1
B. Gubner and Ungerleider[8] $(R_1 + S_3) > 25$	9	2	6 2	98 5	81 0	50 8
C. Goldberger[14] and Schach[22] aV > 11	12	4	8 2	97 3	75 0	51 2
D. Mazzoleni and associates[15] aV > 8	28	12	19 1	91 7	70 0	52 6
E. Noth and co-workers[16] intrinsicoid deflection > 0.05	20	2	13 7	98 5	90 8	53 0
F. Sokolow and Lyon[23] S_V + R or V > 35 or	28	8	19 1	94 4	77 7	53 5
R or V > 26	16	6	11 0	95 7	72 6	53 4
G. Authors R > 18	36	10	24 6	93 1	78 3	54 1
A to F	55	14	37 6	90 4	79 6	58 6
A to G	68	15	46 5	89 6	82 0	62 3

also helpful for critical evaluation of it. The predictive value of a positive or negative finding informs one of the percentage of time that a specific criterion will be correct in the population studied

The criterion of Lewis,[7] $(R + S_3) - (S_1 + R_3) \geq 18$ mm had a sensitivity of 13 per cent and a specificity of 95 7 per cent, and the predictive values of positive and negative findings were 71 1 and 52.1 per cent respectively Gubner's[8] criterion $R_1 + S_3 \geq 25$ mm had a higher specificity of 98.5 per cent at the expense of a 50 per cent drop in sensitivity as compared with Lewis criterion. The specificity of Noth and Myer's[16] criterion intrinsicoid deflection $\geq$ 0.05 seconds, was equally as high as Gubner's,[8] but it maintained a sensitivity of 13 7 per cent and had the highest predictive value of a positive finding of 90.8 per cent. The authors criterion $R_V \geq 18$ mm., had the highest sensitivity of 24 6 per cent and maintained a specificity of 93 1 per cent. Its predictive value of a positive or negative finding of 78.3 and 54 1 per cent was essentially equal to that of the other criteria.

Discussion

The pathological criteria used[17-44] for the diagnosis of LVH varied. The commonly used criteria are left ventricular thickness and total heart weight. The measurement of left ventricular thickness is subject to error depending on the cutting angle at the site of measurement. Obviously the left ventricular wall with an oblique cut will be greater than that with a perpendicular cut. The left ventricular wall at 1 to 2 cm. below the mitral valvular attachment near the anterior septum is several millimeters thicker than at the apex. The thickness varies with the tonus of the myocardium and its state of contraction or relaxation at death. The inclusion of papillary muscles and trabecula

tion in the measurement may also influence the measurement. Thickness of the left ventricular wall of more than 13 mm was used as evidence of LVH; we arbitrarily chose 14 mm as evidence for LVH. The mean left ventricular thickness in this study was 16.8 mm in 163 patients with LVH as compared with 12.9 mm in 145 control subjects.

The total heart weight has been used as evidence of LVH in spite of the fact that it contains various amounts of pericardial fat[12] and short segments of the aorta, pulmonary artery, and veins which may vary from 20 to 60 grams. Hearts that weighed 420 grams or greater were categorized in this study as having LVH. In order to evaluate the influence of body height, weight, or surface area measurements of the ratio of the heart weight to body weight, to body height, and to body surface area were made. In each instance, the LVH group had ratios of 40 to 60 per cent higher than the control group, regardless of sex. These data suggest that for the age group studied heart weight alone is an appropriate indication of LVH. There were minimal differences in body weight or surface area for the age group studied.

The weight limits selected for separating the LVH group from the control group created an intermediate "buffer" group which was evaluated separately. If we assumed that no hearts in the intermediate group had LVH, then 34 per cent had false-positive findings by voltage criteria (Table III). This group no doubt had some hearts which could be classified as having LVH by other pathological criteria.

The ECG has been a useful clinical tool in supporting the diagnosis of LVH. There have been many investigative studies using a specific criterion or combination of criteria in estimating the sensitivity of ECG in making the diagnosis of LVH. Scott and associates[17] and Selzer and colleagues[22,23] reported sensitivities of 85 and 70 per cent, respectively. These studies utilized changes in ST segments and T waves, as well as voltage criteria in their evaluation. In our experience, we have found many changes in ST segments and T waves to be nonspecific; these may be related to electrolyte imbalance, ischemic heart disease, myocardial drugs, hyperventilation, or other conditions. Scott's[17] study reported a high sensitivity of 85 per cent but did not report the specificity of the criterion used—that is, the per cent of control persons tested that were negative. In addition, his sensitivity was influenced by the use of a selective group for analysis wherein each heart and ECG evaluated had LVH confirmed by autopsy. No control study was performed. Obviously, the sensitivity of any criterion for LVH would be increased if all hearts had LVH. Selzer and colleagues[22,23] and Allenstein and Mori[24] included in their study the percentage of false-positive results, which is related to the specificity of a criterion, but the high sensitivity that they reported was partly based on the nonspecific ST-T changes.

The use of ST segment and T wave abnormalities as a criterion for the diagnosis of LVH is highly sensitive. A sensitivity of 67 per cent was shown by Scott and associates.[17] Unfortunately, ST segment depression used as a criterion for the diagnosis of LVH is nonspecific. Rosenfeld and co-workers[1] have found that 63.5 per cent of the false-positive results in their study were secondary to the ST segment criterion. Similarly, T wave changes, isolated or in combination with ST-segment changes, yield a high incidence of false-positive results as reported by Allenstein and Mori.[24] Rochlin and Edwards[9] have found postprandial T wave inversion in normal subjects. We have not evaluated the specificity of ST-T changes in our study because of the lack of specificity of this criterion, especially in elderly patients with coronary ischemic heart disease, degenerative heart disease, and chronic obstructive pulmonary disease.

A prolongation of the Q-T interval as a criterion for LVH was reported by Scott and associates[17] to have a sensitivity of 48 per cent. However, Elek and colleagues,[15] in 120 cases of LVH, found no significant prolongation of the Q-T interval. Changes in the Q-T interval are not specific and are influenced by many factors. Electrolyte imbalance, such as hypokalemia or hypocalcemia, will influence the Q-T interval. Commonly used medications, such

as quinidine and procaine amide, as well as myocardial ischemia or infarction[7] all prolong the Q-T interval.

The use of the intrinsicoid deflection of 0.05 second or greater is highly specific, as demonstrated in our study. However though the specificity was 98.5 per cent this criterion has a low sensitivity of 13.7 per cent. Similar results were reported by Rosenfeld and co-workers[1] and Allenstein and Mori.[18] When ECG evidence for this criterion is present, it would be highly suggestive of LVH even though no other criterion is positive. This criterion of Noth and associates[3] had the highest predictive value of a positive finding (90.8 per cent) in this study.

The voltage criterion of $R_{V6} \geq 18$ mm (1.8 mv.) was chosen because at this voltage we were able to maintain the highest sensitivity of any single voltage criterion and still maintain a specificity of 93.1 per cent. Its predictive value of a positive or negative finding was equal to that of the other criteria. When all the available voltage criteria and the intrinsicoid deflection criterion are used, a maximum sensitivity of 46.5 per cent was obtained. This is far below the sensitivities previously reported by others for the reasons discussed above. We feel that this sensitivity is more representative of the true sensitivity of a group of patients over 40 years of age with the usual array of heart diseases. The collective criteria specificity was 89.6 per cent with a predictive value of a positive finding of 82 per cent and a predictive negative finding of 62.3 per cent.

It is disconcerting that using all the commonly used ECG criteria for LVH we can be significantly accurate in less than half of the cases. Apparently other criteria or other means of evaluation must be sought if we are to improve our diagnostic technique.

Summary

Autopsy data and electrocardiographic findings in 364 unselected cases were studied. 163 cases were classified as having LVH on the basis of heart weight and ventricular wall thickness. 145 patients were classified into a control group, and 56 patients into an intermediate group. The mean age of the 364 patients was 68.5 years. This study compares the commonly used voltage criteria for LVH and evaluates them on the basis of sensitivity, specificity, and predictive values of a positive or negative finding.

Not a single previous voltage or intrinsicoid deflection criterion had a sensitivity greater than 20 per cent of the 163 cases with LVH. The criterion with the greatest sensitivity was that of the authors where R in $V_6 \geq 18$ mm. deflection. This criterion had a sensitivity of 24.[illegible] per cent and a specificity of 93.1 per cent. When all the commonly used voltage criteria were combined with the authors criterion, the diagnosis of LVH could be made in 46.5 per cent of the cases with a specificity of 89.6 per cent, a predictive value of a positive finding of 82 per cent and a predictive value of a negative finding of 62.3 per cent. We feel that $R_{V6} \geq 18$ mm. should be used with other criteria in order to increase the sensitivity and maintain specificity in making the diagnosis of LVH in the age group studied.

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REFERENCES

1. Rosenfeld, I., Goodrich, C., Kassebaum, G., Winston, A. L., and Reader, G.: The electrocardiographic recognition of left ventricular hypertrophy, Am. Heart J. [illegible]:731, 1962.
2. Kilty, S. F., and Lepeschkin, E.: Effect of body build on the QRS voltage of the electrocardiogram in normal men. Its significance in the diagnosis of left ventricular hypertrophy, Circulation 31:77, 1965.
3. Griep, A. H.: Pitfalls in the electrocardiographic diagnosis of left ventricular hypertrophy. A correlative study of 200 autopsied patients, Circulation 20:30, 1959.
4. Kossmann, C. E.: Advances in electrocardiography, New York, 1958, Grune & Stratton, Inc.
5. Holt, D. H., and Spodick, D. H.: The $R_{V6}:R_{V5}$ voltage ratio in left ventricular hypertrophy, Am. Heart J. 63:65, 1962.
6. Okamoto, N., Simonson, E., and Blackburn, H.: The T V_1 > T V_6 pattern for electrocardiographic diagnosis of left ventricular hypertrophy and ischemia. Sensitivity and specificity, Circulation 31:719, 1965.
7. Lewis, T.: Observations upon ventricular hypertrophy with special reference to preponderance of one or other chamber, Heart 5:367, 1914.

8. Gubner R., and Ungerleider H E.: Electrocardiographic criteria of left ventricular hypertrophy Arch. I t. Med. 72 196, 1943
9. Wilson, F N Rosenbaum, F F and Johnson, F D I terpretation of the ventricular complex of the electrocardiogram ventricular hypertrophy in Dock, W and Snapper I editors Advances in internal medicine, Chicago, 1947 Year Book Medical Publishers, Inc. Vol. 2 pp. 37-47
10. Goldberger E. Unipolar lead electrocardiography ed. 2 Philadelphia, 1949 Lea & Febiger P blishers
11. Schach J A. Rosenman, R. H and Katz, L. N The V limb leads in the diagnosis of ventricular strain, Am Heart J 40:696, 1950.
12. Mazzoleni, A., Wolff R. Wolff L., and Reiner L. Correlation between component cardiac weights and electrocardiographic patterns in 185 cases, Circulation 30:808 1964
13. Sokolow M and Lyon, T P The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart J 37:161 1949
14. Noth, P H Myers, G. B and Klein, H. A. The precordial electrocardiogram in left ventricular hypertrophy J Lab. & Clin Med. 32 1517 1947
15. Elek S. R. Silver A. S., Tober J N and Griffith G. C. The Q-T interval in myocardial infarction and left ventricular hypertrophy Am. Heart J 45:80, 1953
16. Vecchio, T J Predictive value of a single diagnostic test in unselected populations, New England J Med. 274 1171 1966.
17. Lipsett, M H and Zinn, W Z. Anatomic and electrocardiographic correlation in combined ventricular hypertrophy Am. Heart J 45:86 1953
18. Fulton, R. M H tchinson, E. O and Morgan, J A. Ventricular weight in cardiac hypertrophy Brit. Heart J 14:413 1952.
19. Zeek, P M Heart weight. I The weight of the normal human heart, Arch. Path. 34:821 1942.
20. Rosahn, P D : The weight of the normal heart in adult males, Yale J Biol. & Med. 14:209 1941
21. Smith H. L. The relation of the weight of the heart to the weight of the body and the weight of the heart to age, Am. Heart J 4:79 1928.
22. Hellerstein, H K. and Santiago-Stevenson, D : Atrophy of the heart: A correlative study of 85 proved cases, Circulation 1:93 1950.
23. Reiner L., Mazzoleni, A. Rodriguez, F L., and Freudenthal, R. R. The weight of the human heart. I Normal" cases, Arch. Path. 68:58, 1959
24. Burch, G. E., Horan, L. G. Ziskind J and Cronvich, J A. A correlative study of post mortem electrocardiographic and spatial vectorcardiographic data in myocardial infarction, Circulation 18:325, 1958.
25. Selzer A., Ebnother C. L., Packard, P Stone, A. O and Quinn, J E. Reliabil ty of electrocardiographic diagnosis of left ventricular hypertrophy Circulation 17:255 1958.
26. Selzer A., Naruse, D Y York, E., Kahn, K. A. and Matthews, H. B Electrocardiographic findings in concentric and eccentric left ventricular hypertrophy Am. Heart J 63:320, 1962.
27. Scott, R. C., Seiwert, V J Simon, D L. and McGuire, J Left ventricular hypertrophy A study of the accuracy of current electrocardiographic criteria when compared with autopsy findings in one hundred cases, Circulation 11:89 1955.
28. Allenstein, B J and Mori, H Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison, Circulation 21:401 1960.
29. Rochlin, I and Edwards, W L. J : The misinterpretation of electrocardiograms with post prandial T wave inversion, Circulation 10:843, 1954.

Basis of the electrocardiogram in right ventricular hypertrophy

Relationship between ventricular depolarization and body surface potentials in dogs with spontaneous RVH—contrasted with normal dogs

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This study was undertaken to determine the basis for the QRS changes produced in the electrocardiogram (ECG) by right ventricular hypertrophy (RVH). Previous observations by Durrer and associates[1] and others[2-4] have indicated that there is a delay in epicardial activation of the hypertrophied right ventricle. A study of the transmural activation of the heart in dogs with surgically produced atrial septal defects[5] demonstrated prolonged intramural activity due to an increased right ventricular mass, resulting in terminal QRS changes.

Recent studies by Taccardi, Horan and co-workers, and the authors[11,12] have demonstrated nondipolar patterns of body surface voltage distribution. In addition, it has been shown that the nondipolarity reveals details of localized cardiac activity during depolarization.[11] It follows that the potentials obtained from multiple torso leads may also produce more information about the electrical activity and cardiac structure in RVH.

To demonstrate the relationships between various methods of displaying the surface ECG (i.e., ECG, VCG, surface maps, etc.) as well as to present the correlation between surface ECG data and the heart's activity, the fundamental "sources" of the electric field must be examined simultaneously with the surface potentials. For this reason isopotential surface maps and vectorcardiograms (VCG's) have been correlated in time in dogs with spontaneous RVH. Also, both the maps and the loops have been correlated with the heart's activity by time alignment of ventricular excitation with the surface potentials.

It is the purpose of this report to demonstrate the following: (1) the basis for the abnormal surface potentials during ventricular depolarization (QRS) and also dur

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ing the period of early repolarization (S-T) in dogs with spontaneous RVH (2) details of the intramural and epicardial ventricular excitation including the mechanism of delay of epicardial excitation in the right ventricle as well as the pattern and rate of spread of activity in this hypertrophied structure and (3) the degree to which the electrical events within the heart are represented on the body surface in equipotential maps as compared to VCG's in RVH

Methods

Five dogs with spontaneous RVH were studied Three of the animals had congenital subpulmonary stenosis and 2 of the dogs had double outlet right ventricle with pulmonary outflow obstruction[13] In 2 of the dogs with subpulmonary stenosis right ventricular peak systolic pressure was in excess of 150 mm Hg and in the third animal the peak right ventricular systolic pressure was 80 mm Hg In the 2 animals with double outlet right ventricle the right ventricular pressures were at systemic level due to a large ventricular septal defect These animals were part of a larger series of dogs with congenital heart disease from the Comparative Cardiovascular Studies Unit of the University of Pennsylvania School of Veterinary Medicine. In addition to routine cardiac catheterization data, selective venous angiocardiograms were recorded for 3 of the animals and biplane cineangiocardiograms were recorded for 2. In all animals all diagnoses ultimately were confirmed by postmortem studies.

The relationship between body surface potentials and ventricular depolarization has been reported previously [7-14] In this paper these data are presented for one representative normal dog for contrast with the RVH data.

Vectorcardiographic methods Corrected VCG's were recorded for all animals using the lead system for the dog of McFee and Parungao.[11] Because of the small number of dogs, no attempt was made to evaluate the VCG data statistically

Methods of producing isopotential maps Methods for the determination of equipotential maps of body surface voltage distribution have been described in detail previously [11,14] Using an Ampex DAS-100 system 5 thoracic ECG's were tape recorded together with a constant time reference tracing A total of 200 high fidelity tracings were recorded from points previously identified on the dog's torso. The data was recorded in 40 separate time segments, each segment consisting of 5 simultaneous ECG's and the constant time

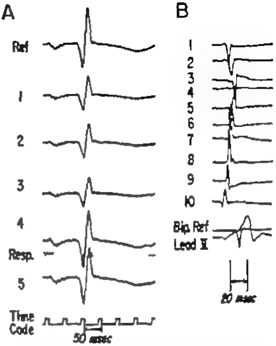

Fig 1 The analogue data
A Body surface potentials 5 simultaneous, high fidelity electrocardiographic signals were recorded from the body surface together with a constant time reference tracing Respiratory variation were monitored with an impedance respirometer and time code was generated for locating data to be processed for the digital computer All data was selected in the resting phase of expiration A digital computer program was used to synchronize all data in time and to calculate instantaneous potentials for the 200 positions for each millisecond of QRS. *B* Ventricular activation bipolar potentials 10 simultaneous bipolar potentials were recorded across the ventricular walls from the transmural plunge electrodes. A total of 14 bipolar recordings were obtained for each electrode insertion from 15 terminals on the electrode. A constant bipolar tracing was simultaneously obtained with each electrode position recorded therefore all activation data could be time aligned through this reference signal. The time of arrival of depolarization in local areas of the myocardium was determined from the peaks of the bipolar complexes recorded from points on the electrodes in contact with these ventricular regions. Maps of the sequence of epicardial *and transmural ventricular depolarization* (Fig 9) were constructed for specific instants by connecting the points of equal excitation time

reference tracing (Fig. 1,*A*). Time alignment of the 40 segments of 5 tracings each was accomplished by relating them to the instant of base-line crossing of the intrinsicoid deflection in the time reference tracing.

The recording system included lead isolation through cathode followers with unity gain. The frequency response of the system was flat to 1,250 c.p.s. During data acquisition, the tape output was monitored by a Honeywell Visicorder oscillograph for editing purposes. Respiration was monitored with an impedence respirometer. Only beats occurring in the expiratory pause were analyzed.

Data editing was performed by review of the photographically recorded tracings and identified by relating the ECG signals to the time code. The selected data was then processed automatically for input to an IBM 7072 digital computer using an AIL analogue to digital converter at a sampling rate of 926 samples per channel per second. Using the time of base line crossing of the intrinsicoid deflection for time localization, voltages of all 200 tracings were measured in reference to base-line potential (P-R segment for each millisecond). The output of the computer was presented in a geometric format of voltages for all surface points at specified instants related in time to the reference tracing. Instantaneous equipotential maps of body surface voltage distribution were produced for every 1.08 msec. of QRS.

Ventricular activation methods. Epicardial ventricular excitation data were recorded with a bipolar electrode according to the method of Venerose and associates. Subsequently, transmural ventricular activation data were obtained with Scher plunge electrodes.[17] The methods have been described in detail elsewhere.[-19] Bipolar epicardial potentials were recorded from 30 to 50 points on the surface of the right and left ventricles. Plunge electrodes were then placed in the ventricular walls and both unipolar and bipolar potentials were recorded from the 15 terminals of each electrode. Twelve type FM 12 Tektronix preamplifier were used to record 15 channels of data from one electrode together with the time reference bipolar electrogram and Lead II ECG. The analogue signals were recorded on photographic paper by a Heiland visicorder oscillograph. The paper speed was 500 mm. per second. Thirty to 60 electrodes were used in a single study and were initially placed in the free walls and subsequently advanced into and across the septum. Time alignment of all excitation data was accomplished by relating all bipolar tracings to the constant time reference bipolar electrogram (Fig. 1,*B*).

At the completion of each activation study, transmural electrode tracts were permanently identified by drawing coded multicolored threads through the electrode tracts. The hearts were cut into 4 sections and a quantitative outline of each section was formed by printing an inked impression of the section onto paper. Electrode tracts were then drawn in on the impression.

Instantaneous maps of the dipole layer distributions in the ventricles were constructed for intervals prechosen to relate to surface data, i.e., VCG, isopotential surface maps, etc., by connecting all points for a specified time on different electrodes (see Fig. 9).

Correlation of surface potential data and activation data

TIME ALIGNMENT OF VCG'S AND EQUIPOTENTIAL MAPS. Correlation in time between vectorcardiograms and surface maps were performed as follows: (1) Standard Lead II was recorded simultaneously with the X, Y, Z leads of the VCG. (2) Lead II was again recorded with the time reference tracing of the surface map. (3) By relating the 2 Lead II tracings, deflections of the VCG were time aligned with instantaneous isopotential surface maps.

TIME ALIGNMENT OF SURFACE DATA WITH ACTIVATION DATA. Both VCG's and equipotential surface maps were correlated in time with epicardial and transmural ventricular activation as follows: (1) Standard Lead II was recorded simultaneously with the time reference bipolar electrogram during ventricular activation. (2) Local excitation times were then related to the VCG's and surface maps through Lead II.

Results

The data from 1 representative normal dog (Figs. 2, 5, 6, and 12), 1 dog with RVH due to subpulmonary stenosis with intact ventricular septum (Figs. 3, 7, 8, and 13), and 1 dog with a double outlet right ven-

tricle and RVH (Figs. 4 9 and 10) are presented. The results are presented in a format of illustrations so that correlations of different data in the same dogs are possible and also, so that comparisons between the normal data and the 2 different types of RVH are possible.

Body surface potentials in the normal dog Four successive equipotential maps are illustrated for a normal dog on a model torso in Fig 2,*A* through *D* The instantaneous surface potentials are time aligned with the frontal and left sagittal VCG The dog s torso is viewed from a slight left oblique position. The positive potentials, in relationship to average potential[11] are indicated by the darker areas the negative potentials by the lighter regions. A maximum is defined as an area in which the potential is higher (more positive) than in surrounding regions and a minimum indicates a region in which the potential is lower (more negative) than in adjacent regions. Nondipolarity* of the surface potential distributions is indicated by the irregular contours, pseudopods and multiple discreet maxima and minima. The line of average potential ("null line") is indicated by the boundary between dark and light areas.

In *A* at 11 msec., the maximum was located anteriorly and slightly inferior in relationship to the minimum. The VCG was displaced anteriorly at this instant. In *B* at 22 msec., the central region of the torso was invaded by a pseudopod of negative potential. The potential distribution was *quite nondipolar at this instant as demonstrated* by marked irregularity of contour and 2 discreet minima separated by a "relative maximum (the saddle described by Taccardi[7]) The VCG reached the point of greatest inferior displacement during this interval In *C* at 27 msec., the maximum had moved laterally and posterior and the anterior chest was invaded by a single minimum. However there was still considerable nondipolarity as manifested by the pseudopodlike contour of the equipotential lines. In *D* at 32 msec. the maximum was located posteriorly and the minimum anteriorly and centrally

By inspection of the 4 instants demonstrated in this figure it can be seen that the maximum and minimum rotate through an arc which is approximated by the plane of the loop Observe that although map *A* and *D* display some semblance of dipolar symmetry all of the equipotential contours are significantly irregular (especially *B* and *C* instants) and contain either irregular contours, considerable pseudopod formation or discreet, multiple maxima or minima.

Body surface potentials in subpulmonary stenosis and marked RVH Fig 3,*A* through *D* demonstrates 4 successive equipotential maps for a dog with subpulmonary stenosis, intact ventricular septum and marked RVH The VCG s and surface potential distributions were remarkably similar in both animals with this abnormality In *A* at 16 msec. the maximum was located anteriorly and slightly inferior in relationship to the minimum The potential distribution at this instant was somewhat similar to the map of the normal dog between 11 to 15 msec. (Fig 2,*A*) This period was associated with the greatest anterior inferior displacement in the VCG The degree of apparent nondipolarity as manifested by *the irregularity of the contour* lines at this instant was slight as compared to the succeeding instants.

In *B* at 24 msec. there was a pseudopod of negative potential projecting from the left lower thorax. This gradient of negative potential had moved upward toward this location beginning at the left inferior portion of the torso. There were 2 minima with an intervening region of positive potential and the over all distribution was highly nondipolar With the movement of the negative potentials into the central chest anteriorly the VCG proceeded in a clockwise arc to the right, superiorly and posterior as viewed from the front. In *C* at 33 msec., the maximum had moved superiorly (cranially) and was located to the right of

*The terms dipolar and nondipolar are used descriptively in this report. Dipolar body surface maps are defined as distributions consisting of a single maximum and minimum of potential and relatively smooth isopotential contour lines as illustrated in Fig. 2,*A*

Nondipolar is used to mean multiple maxima or minima and, or marked irregularity of isopotential contour characterized by pseudopod formation as illustrated in Fig 2,*B* and *C*. The pseudopodlike equipotential contour lines associated with large gradients are due to irregular discontinuities (openings or boundaries) in those portions of the depolarization distribution proximal to the torso which are projected onto the body surface (Figs. 2,*B* and 12,*C* and 3,*B* and 12,*A*).

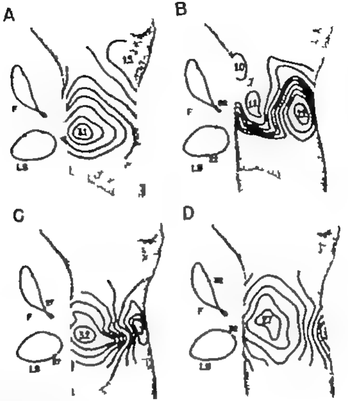

Fig. 2. Equipotential maps and VCG in normal dog.
The isopotential distributions for 4 successive instants during QRS (11, 22, 27, and 32 msec.) are shown in *A*, *B*, *C*, and *D*, respectively. The dog's torso is viewed from a slight left oblique position. Dark areas indicate positive potential, light areas negative potential. The potential distributions at 11 and 32 msec. were the most dipolar, while those at 22 and 27 msec. were very nondipolar as characterized by pseudopodlike isopotential contours and multiple maxima and minima. The frontal (*F*) and left sagittal (*LS*) McFee corrected VCG's are correlated in time with the maps. Observe that the arc through which the potentials move in the maps determines the plane and direction of rotation of the loop. The potentials are initially positive anteriorly. Subsequently, a pseudopod of negative potential moved into the presternal region displacing the maximum laterally and inferiorly. The 2 islands of negative potential (the 2 minima) at 22 msec. were characteristic of all normal dogs for this period of QRS (map *B*). The maximum continued laterally and posterior and was replaced anteriorly by the minimum correlating with the inferior, lateral, and posterior displacement of the VCG (*C* and *D*).

the central thorax. The VCG demonstrated further superior posterior displacement to the right. In *D*, at 48 msec., the maximum had moved to the left completing a clockwise arc. *As indicated in this figure, the VCG terminated during this interval; however, body surface potentials representative of ventricular excitation persisted for an additional 4 msec.*

The time-course and distribution of the body surface potentials in the 2 dogs with marked RVH secondary to subpulmonary stenosis were in marked contrast to that of the normal dogs studied. The clockwise movement of the maximum with the pseudopod of negativity invading the anterior thorax from the inferior left chest region was characteristic of both of these animals, as was the clockwise, rightward superior posterior displacement in the VCG. Also, the equipotential contours demonstrated more obvious nondipolarity than in the normal dog beginning with the emergence of the pseudopod of negativity over the left chest at 24 msec. from onset.

The body surface potentials in double outlet right ventricle and marked RVH. Fig. 4,*A* through *D* illustrates the equipotential distribution and frontal and left sagittal VCG for 1 of the 2 dogs in this category. Both the time-course and distribution of surface

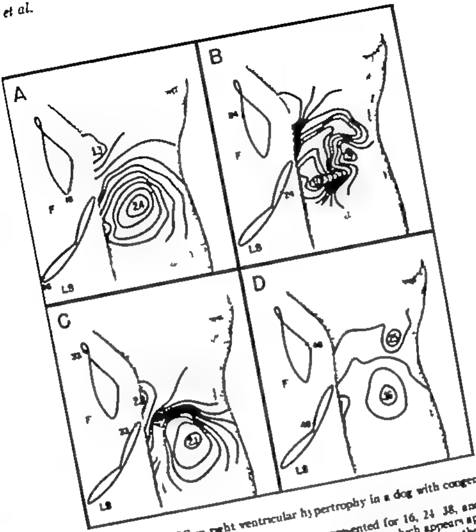

Fig. 3. Equipotential maps and VCG in right ventricular hypertrophy in a dog with congenital subpulmonary stenosis.

Isopotential maps and frontal and left sagittal VCG are presented for 16, 24, 38, and 48 msec. in A, B, C, and D, respectively. The format is the same as in Fig. 2. The only map which appears approximately dipolar is D; the others are all primarily nondipolar. Note that in contrast to the normal dog, the pseudopod of negativity moved to the central sternal region from the dog's left side. The maximum moved to the right and superiorly in a clockwise arc, and this correlated with the clockwise rotation of the QRS loop in the frontal plane. The sequence of movement of the maximum and minimum was principally over the anterior (and lateral) surfaces of the torso in contrast to the anterior to posterior time course in the normal dog. This correlated with the tendency of the loop to lie in the ... (frontal) plane as opposed to the sagittal plane in normal dogs.

potentials as well as the VCG were quite similar in these 2 animals.

In A, at 25 msec., a posterior lateral pseudopod of negative potential started to project into the maximum which had been building up over the anterior thorax since the onset of QRS. At this time the VCG demonstrated the beginning of rightward displacement. In B, at 40 msec., the maximum was displaced rightward and laterally over the torso. Pseudopods of negative potential projected into the central region of the torso creating considerable nondipolarity. The VCG was displaced rightward. In C, at 49 msec., the potentials are viewed from the right oblique aspect of the torso. The region of positive potential formed a band of diminishing voltage over the right lateral chest. The VCG exhibited decreasing voltage in the X-axis. In D, at 57 msec., both right and left oblique views are illustrated. Two islands of positive potential over the upper anterior and lower right lateral thorax were present; they gradually diminished over the succeeding 4 msec. During the interval between 57 and 61 msec., the displacement of the vector cardiographic loop was contributed to by

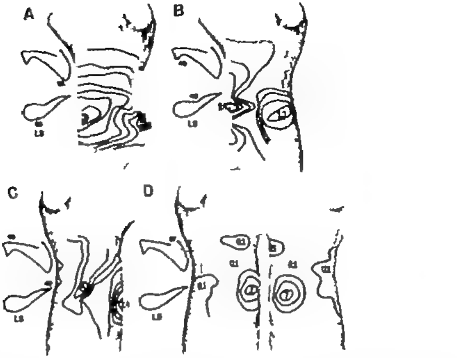

Fig. 4. Equipotential maps and VCG in right ventricular hypertrophy in dog with double outlet right ventricle. Isopotential maps and the frontal and left sagittal VCG are presented for 25, 40, 49, and 57 msec in *A* through *D*. *D* 1, *D* 2 perspectives of the dog's torso are presented to view the potentials on the left and right lateral chest surfaces. As in the dog with subpulmonary stenosis (Fig. 4,*A*) the onset of considerable nondipolarity began with the appearance of the negative pseudopod pushing in to the central area of the torso. However, in contrast to the dogs with subpulmonary stenosis, the island of negative voltage began posterolaterally rather than anterolaterally and subsequently as shown in *B* and *C*, the maximum moved in a wide band to the right and laterally. These changes in potential were accompanied by the anterior and rightward inscription of the loop without superior displacement. During terminal QRS, 2 maxima were present over the right, anterior and lateral thorax (Fig. 4,*D*). These islands of positive potential persisted for 4 msec after the apparent end of QRS as manifested by the loop. The central minimum and left posterior maximum also indicated in *D* persisted after the termination of the 2 depolarization maxima on the right side of the dog's torso. This multipolar distribution represented the effect of simultaneous depolarization and repolarization on the equipotentials during QRS (depolarization). The abnormal repolarization potentials resulted in failure of the loop to return to the zero point and caused S-T segment displacement in the scalar ECG's.

an admixture of surface potentials generated by both ventricular depolarization and repolarization. The anterior minimum and left posterior-lateral maximum progressively increased in intensity in subsequent surface maps as the 2 maxima reflecting depolarization disappeared.

A comparison of the surface potential distributions and VCG's during QRS in the 2 groups of dogs with RVH indicated a specific distribution and time-course in each of the 2 categories. The differences in vectorcardiographic displacement in the 2 groups could be correlated with the characteristic sequence of potential distribution. For example, in the 2 dogs with double outlet right ventricle (Fig. 4) there was no terminal superior displacement in the VCG as was noted in the 2 dogs with subpulmonary stenosis (Fig. 3). This difference correlated with the movement of positive potentials from left to right in the dogs with double outlet right ventricle (Fig. 4) as compared with the inferior-superior movement of the maximum in the dogs with subpulmonary stenosis (Fig. 3).

The failure of the loop to close (ST shift) was caused by the prominent anterior minimum and left posterior lateral maximum which developed during terminal QRS and

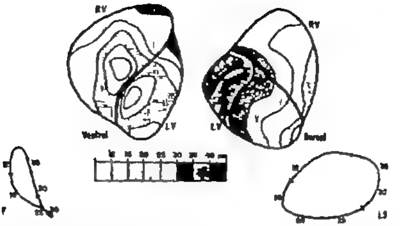

Fig. 5. Normal epicardial ventricular depolarization.

The pattern of epicardial excitation (breakthrough) is indicated above, and the ventricular activation time is indicated by the accompanying graph. Epicardial breakthrough occurred initially in the anterior right ventricle near the interventricular sulcus and spread centrifugally. The pulmonary conus region was activated at [illegible] msec. and the basal left ventricle at [illegible] msec. in this dog. There was a relatively late area of excitation in this animal on the lower anterior left ventricle near the interventricular sulcus. Whereas there were variations in the details of epicardial spread, the general pattern was quite similar. The frontal (*F*) and left sagittal (*LS*) VCG's are presented for time correlation with the epicardial data. Note that the loop tends to lie in the Y Z (sagittal) plane. This orientation resulted from the effect of the anterior posterior unbalancing of forces due to (1) the posterior opening in the distribution of excitation during the first *15* msec. of depolarization (see Fig. 6) and subsequently (*2*) the anterior opening in excitation fronts with epicardial breakthrough beginning in the center of the cardiac mass and progressing almost symmetrically lateral and posterior.

persisted after the end of ventricular depolarization (QRS). These potentials were the result of abnormally intense repolarization currents which began before the end of depolarization.

Ventricular excitation

THE NORMAL DOG. Fig. 5 illustrates the epicardial sequence map of ventricular excitation in a normal dog. The ventral (anterior) aspect of the dog's heart is viewed in the figure on the left and the dorsal or diaphragmatic surface on the right. In the figure on the left, the longitudinal axis of the dog is oriented vertically, the heart is viewed frontally and is tilted to approximate the actual anatomic position within the torso. The interventricular sulcus is indicated by the dark line (separating the 2 ventricular masses). The time of epicardial ventricular excitation for the normal dog is indicated by the graph below. The time of earliest epicardial activity in this animal was noted at 10 msec. after the onset of the reference VCG. The pattern of epicardial spread was basically similar in all normal dogs studied. The earliest site of epicardial activity (breakthrough) was observed in the midright ventricle near the interventricular sulcus. This activity spread centrifugally toward the atrioventricular groove, the inflow and outflow (conus) regions of the right ventricle, and leftward across the interventricular sulcus. The outflow tract was frequently the latest region to activate on the right ventricle. However, later regions were usually found near the base of the left ventricle as in this animal. In several of the normal animals, late activation of the right ventricle occurred over a wide area encompassing inflow and outflow regions adjacent to the atrioventricular sulcus. The pattern of epicardial spread was considerably more irregular than previously reported.[1,2] This irregularity indicated by the pattern of the isochronous contours demonstrated in Figs. 5 and [illegible] resulted from the greater accuracy attained by sampling more points on the epicardium. Additionally, early breakthrough near the left ventricular apex was frequently noted, however, it was always preceded by earlier epicardial activity in the right ventricle. An area of relatively late excitation was frequently noted on the left side, near the interventricular sulcus anteriorly. Finally, there were variations in

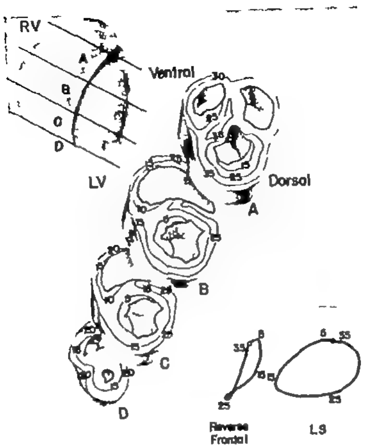

Fig. 6. Normal transmural ventricular depolarization and the VCG.

The 4 sections of the heart have been turned 160 degrees in order to view the transmural sequence of activation. Three-dimensional electromotive surfaces can be realized by mentally connecting the fronts of equal time in the 4 sections. The instants of time to be represented were chosen from surface data (i.e., VCG and surface maps) for distinctive periods of excitation. The frontal VCG is reversed so that it can be correlated spatially and temporally with the transmural activation data.

Note, that at 15 msec., the circumferentially distributed electromotive surface was open dorsally at the mitral annulus; this resulted in the anterior vectorcardiographic displacement. The apex to base (anterior to posterior) excitation of the left ventricle dominated the remainder of QRS producing the inferior then posterior displacement in the VCG. This left free wall predominance was the result of earlier termination septal and right free wall activity. The site of earliest activity was in the mid left septum and anterior left ventricular endocardium at 5 msec. The latest region was located in the basal section (section *d*) in that portion of the septum adjacent to the septal band of the crista supraventricularis.

the pattern described above with excitation of the outflow (conus) region of the right ventricle occasionally occurring later and thus, simultaneous with epicardial excitation of the basal left ventricle. Also there were minor variations in the exact region of the right ventricular breakthrough. However the general order of epicardial excitation was quite consistent in over 30 normal dogs and was of the type shown in Fig. 5.

The transmural sequence of excitation in a normal dog is illustrated in Fig. 6. The process of activation is time aligned with the dog's VCG. In this figure, 4 sections of the heart are illustrated and have been turned approximately 160 degrees (in relationship to the anterior view at the upper left of the figure) about an axis passing vertically through the heart. Note that the apex of the left ventricle which was oriented toward the viewer in the figure at the upper left is directed away from the viewer in the 4 sections presented to show the transmural distribution of activation. Because of

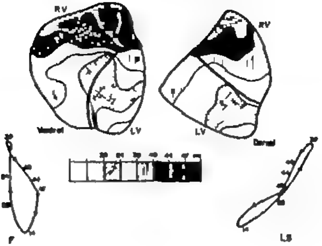

Fig. 7. Epicardial ventricular depolarization in right ventricular hypertrophy due to subpulmonary stenosis. The presentation is the same as in Fig. 6. Note that initial epicardial breakthrough occurred near the apex of the left ventricle. The subsequent sequence was from left to right ventricle. If the right ventricle was examined as an isolated structure, the pattern of epicardial spread was not remarkedly different from normal. However, breakthrough in this region was late when compared to the onset of left ventricular epicardial activity and the mechanism is indicated in the transmural data (Fig. 8). The clockwise rotation of the QRS loop is related to the clockwise sequence of ventricular depolarization. The loop was oriented principally in the frontal plane; this correlates with the balancing of activation in this plane subsequent to breakthrough over the left ventricle with unopposed excitation front oriented parallel to the X and Y axes.

thus spatial rotation of the heart the frontal VCG is presented in the reverse in order that correlations between activation and the VCG may be carried out in space as well as in time. Details of the events of transmural activation have been previously reported by Scher and Young,[7] Durrer and colleagues,[11] and the authors.[7,18] Only a few selected instants of activity are presented in this figure.

Earliest activity was usually noted in the left septum in the lower 2/3 or 1/2 of the ventricular mass as noted in this animal. Initial right ventricular activity usually occurred 3 to 5 msec. later in the right free wall. Several studies of the Purkinje distribution to the right and left ventricle have demonstrated very little Purkinje tissue on the right septal surface posterior to the trabecular region of the septum at the point of juncture of the right ventricular free wall.[19] This portion of the anterior trabecular septum activates almost simultaneously with that of the free wall supplied by the false tendons of Purkinje spanning the right ventricular cavity. Because of the manner in which the Purkinje system is distributed on the right side, right to left septal activation proceeded from the ventral corner dorsally (anterior to posterior) at a relatively slow rate as compared to the left to right activity progressing from the left side. The Purkinje network on the left side has been observed to supply the left septal surface widely over its lower 2/3 and accounts for the broad wave of activity progressing from left to right. Double septal envelopment began in the ventral (anterior) septum and progressed toward the dorsal (posterior) septum.

The latest area to be depolarized was in the mass between the outflow tract of the right ventricle and basal region of the left ventricle as indicated in Section A of Fig. 6. The anatomy of this area was somewhat more complex than the rest of the myocardium. The inflow and outflow tracts of the right ventricle were separated by the crista supraventricularis and its parietal reflection onto the free wall. The septal reflection of the crista together with the abrupt increase in mass of myocardium in the anterior left ventricle near the interventricular sulcus at the heart base formed a thick mass of muscle between right ventricular outflow (pulmonary conus) and left

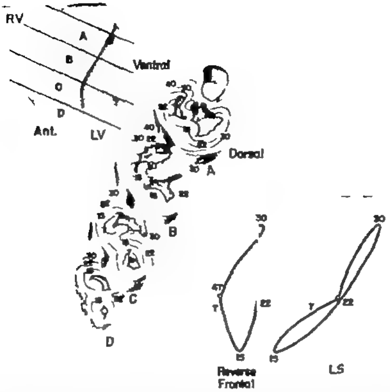

Fig. 8. Transmural ventricular depolarization in right ventricular hypertrophy due to subpulmonary stenosis. The presentation is the same as in Fig. 6. The pattern of initial depolarization was similar to the normal dog presented in Fig. 6. Note that at 15 msec. the cone of activity surrounding the cavities and open in the basal section produced a similar vectorcardiographic displacement to that observed in the normal animal. Breakthrough of wavefronts occurred first in the left ventricle as contrasted to initial right ventricular breakthrough normally. The thickened right ventricle permitted a greater surface area of the obliquely positioned dipole layer. Maximum superior displacement in the VCG (30 msec.) correlated with the period of maximum area of unopposed excitation fronts in the right ventricle. Due to increased mass of the right ventricle its excitation time was prolonged resulting in delay of epicardial excitation (epicardial breakthrough).

ventricular base. Because of the distance of this mass from both Purkinje networks it was usually last to be excited in a region located centrally between the 2 cavities. This was consistently the latest region of activation in dogs in which electrodes were passed into this area from the ventral (anterior) base of the heart.

VENTRICULAR ACTIVATION IN RVH.

1. Ventricular Excitation in Dogs with Subpulmonary Stenosis. Fig. 7 illustrates the map of epicardial ventricular excitation for 1 of the 2 dogs with severe RVH due to subpulmonary stenosis. The earliest point of epicardial excitation or breakthrough was noted at the apex of the left ventricle. This correlated with the thinnest area of either ventricle and represented the closest epicardial location in relationship to a Purkinje network. The general order of spread was from below upward and from left ventricle to right ventricle. The *sequence* of epicardial excitation of the right ventricle was not unlike the normal heart when viewed as an isolated structure. As in normal dogs the earliest site of epicardial breakthrough was near the midportion of the right ventricle, close to the interventricular sulcus with activity progressing laterally toward the atrioventricular sulcus and upward to the outflow tract. However the earliest point on the right ventricle, although located in the same region as in the normal dog, was 14 to 15 msec. later than normal. Observations of the total (left and right ventricle) epicardial activity

combined with the transmural data presented in Fig 8 demonstrated the mechanism of this delay

Fig 8 illustrates the transmural ventricular excitation in this dog The periods of excitation are again related to specific vectorcardiographic intervals and as in Fig 6 the frontal VCG has been reversed The conduction velocity through the walls and septum varied between 0 3 to 0 5 meters per second depending upon the region examined and was normal for this laboratory There was no delay noted in endocardial activation times of the right ventricle indicating an absence of a disturbance in impulse propagation (bundle branch block) Ventricular depolarization was prolonged in the ventricular septum This was the result of an increased upper septal mass caused by the hypertrophy of the septal band of the crista supraventricularis.

The reason for the delay in the epicardial excitation times is apparent from analysis of the intramural data. As shown in Fig 8 at 15 msec. activity surrounded both cavities. By mentally constructing a three-dimensional surface of activity for the 15 msec. instant from the 4 sections of Fig 8 it was observed that 2 circumferential cones surrounded the ventricular cavities coalescing only in Section *C* Due to the natural cardiac boundaries formed by the inflow regions of the ventricles (mitral and tricuspid valve areas) these cones were open at the cardiac base and closed at the apex in Section *D* At 22 msec. of activity epi

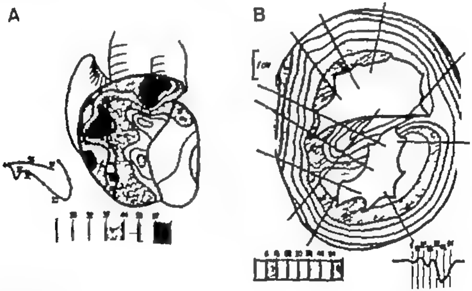

Fig 9 Epicardial and transmural ventricular depolarization in right ventricular hypertrophy due to double outlet right ventricle

A The sequence of epicardial ventricular depolarization is depicted for several instants on the anterior surface of the ventricles. The time of local excitation is indicated below The earliest point of epicardial activity (breakthrough) occurred posteriorly at 22 msec. and at [illegible] msec. activity was present laterally over the left ventricle. Also, at 25 msec. breakthrough of excitation was present at 2 sites on the epicardium of the right ventricle Note the inhomogeneity of spread of the excitation over the right ventricle with the wide boundary of activity progressing laterally toward the atrioventricular margin. The latest regions to be excited are indicated in black By referring to Fig 4 the sequence of body surface potential change can be correlated with the sequence of excitation. The event of epicardial breakthrough over the posterior lateral left ventricle could be predicted from the surface map at 25 msec. The characteristics of the spread of excitation over the anterior surface of the ventricles in a left to right direction, as well as terminal depolarization over a wide region along the atrioventricular margin of the right ventricle could also be predicted from the surface maps. *B* The sequence of transmural ventricular depolarization *is depicted for one cross section of this heart*. The tracts of the plunge electrodes are illustrated and the time of local depolarization is indicated in the graph below The *Lead II* scalar ECG is also presented for time reference Note the thickness of the right ventricle and the similar conduction velocity in the right and left ventricles The conduction velocity was normal in the right ventricle with activity taking longer to spread through this thick structure

cardial breakthrough first began in the apical and anterior portions of the left ventricle and proceeded from left to right and from below upward. The delay in right ventricular epicardial activity was a function of the increased right ventricular free wall thickness, and there was no evidence of abnormally retarded conduction through the wall.

2. Ventricular Excitation in the Dogs with Double Outlet Right Ventricle. Fig. 9,A illustrates the epicardial excitation sequence of the ventral (anterior) surface of the heart in 1 of the 2 dogs with double outlet right ventricle. The site of initial epicardial breakthrough in the dog whose data is presented here, was posteriorly in the left ventricle and occurred at 20 msec. By 25 msec. the breakthrough was observed laterally over the left ventricle, and at 2 sites in the right ventricular free wall near the interventricular sulcus. Although the sequence of epicardial excitation occurred from left ventricle to right ventricle as in the first group of dogs with RVH and intact ventricular septum the details of right ventricular excitation in the latter group were different from the former dogs. The pattern was essentially the same in both dogs in this latter category and as

Fig. 10. Transmural ventricular depolarization and the VCG in right ventricular hypertrophy in the dog with double outlet right ventricle.

The heart has been cut into 4 sections parallel to the base and transmural depolarization is indicated for selected instants on the undersurface of 3 of the sections. The VSD is indicated by the asterisk ( ). At 20 msec. excitation fronts surrounded the ventricular cavities and formed a three-dimensional cone-like surface, open at the heart base and closed at the apex. This distribution of excitation produced the anterior inferior spatial displacement in the VCG corresponding to the spatial orientation of the base to apex axis of the heart.

At 40 msec. breakthrough of activation at the epicardial surface of the left ventricle resulted in a wide unopposed excitation front in the right ventricle; this produced the rightward vectorcardiographic displacement. By 50 msec. the total area of the wavefronts in the right ventricle was less than at 40 msec. and there was decreasing spatial voltages in the loop.

observed in Fig 9,*A* a large part of the atrioventricular margin of the right ventricle was activated late Terminal activity was located at both extremes of this margin in inflow and outflow (conus) regions in contrast to terminal excitation of the conus region of the right ventricle in the dogs with subpulmonary stenosis, Fig 7

A detailed map of the transmural activation for 1 section of the heart of a dog with double outlet right ventricle is illustrated in Fig 9 *B* The isochronous surfaces which indicate local activation times in the myocardium were constructed from bipolar potentials recorded from the electrodes whose tracts are indicated Note that the endocardial excitation time in the right ventricle was not delayed There was no evidence of abnormal conduction velocity in the right ventricular free wall The rate of excitation in the different parts of the ventricle varied between 0.3 to 0 5 meters per second as demonstrated by this illustration The variation in spread appeared to correlate with the asymmetry of the Purkinje distribution Although a geometric anisotropy related to myocardial fiber orientation may have been a factor this was not specifically investigated

Fig 10 illustrates the transmural activation data for the dog with double outlet right ventricle correlated with the VCG The heart at the upper right has been cut into 4 sections and the transmural ventricular activity has been depicted in 3 of the sections on the bottom surfaces. The position of the VSD is indicated in the upper section by the asterisk Observe that at 22 msec electromotive surfaces surrounded the 2 ventricular cavities in the lower sections. Subsequently breakthrough occurred in the left ventricle resulting in large unopposed activation fronts in the right ventricle At 50 msec., there was a decrease in the total area occupied by activity in the right ventricle A frontal perspective of the spatial VCG is presented for correlation.

Discussion

Limitations of the methods

1 ISOPOTENTIAL MAPS The 2 primary considerations in the construction of isopotential maps are the noise level and phase shifts due to difficulty in precisely synchronizing all 200 channels of data From inspection of the base line during the P R interval (in maps prior to the onset of QRS) the variations in signals seldom exceeds ± 60 microvolts. The nonsimultaneous sampling technique may produce phase shifts between groups of 5 electrodes resulting in adventitious gradients. Although simultaneous sampling of all 200 points would eliminate this problem it is not feasible at present Since the rate of analogue-to-digital conversion (926 samples per channel per second in this laboratory) determines the frequency with which the analogue signal is sampled the more rapid the conversion rate the less will be the phase error Digital interpolation between points sampled during QRS might also be used to minimize phase error resulting from nonsimultaneous recording of potentials.

2 VENTRICULAR EXCITATION The factor of nonsimultaneous sampling of the ventricular excitation data necessitates the time alignment of the signals from numerous electrode insertions Although changes in the ventricular excitation program over a period of several hours might produce spurious results, the assumption is made that all activation cycles are the same. Extensive experience with this type of study indicates that the heart preparation is quite stable for several hours and changes can be recognized by altered configuration of the reference Lead II and the reference bipolar tracing and by comparing data recorded early and late in the experiment from the same electrode insertion

3 THE CORRELATION OF BODY SURFACE POTENTIAL AND VCG'S WITH VENTRICULAR ACTIVATION The techniques used to time align the excitation and surface data may result in an initial phase dissociation which remains constant for all successive instants of the correlation This has been estimated to be ± 2 msec.

The correlation of body surface potentials with ventricular excitation in the normal dog There is a fundamental relationship between the heart's structure the sequence and distribution of ventricular excitation the configuration of the electric field produced by the generators during excitation and the time course and distribution of the potentials recorded on the body surface To understand the effect of ventricular

activation on the distribution of surface potentials and to appreciate the significance of the information obtained by a particular technique of displaying surface voltage (i.e. VCG ECG or surface maps) internal and external data must be correlated in time and space. Of importance is the finding that the generator configuration can be correlated with the distribution of surface potentials[11] even though the equipotential contours are considerably influenced by the irregular shape of the torso and the eccentric position of the heart. The distorting effect on the surface potentials produced by the configuration of the torso although not constant is very similar in each species (dog and man)

A useful approximation in examining the relationship between the distribution of depolarization and body surface potentials is to consider the surface of activation as composed of many dipole generators in which the current density is uniform over the generator surface. Thus assuming a uniform dipole layer a closed surface of activity produces no net current and no change of potentials in or on the torso surrounding the generators. In this model

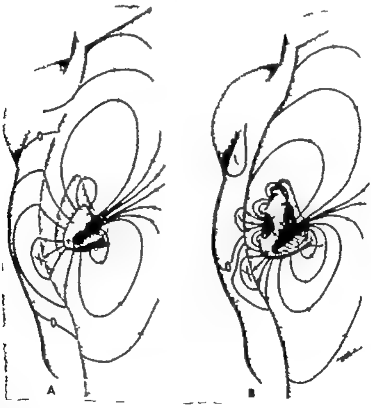

Fig. 11 Relationship between body surface potential distribution and the discontinuities of the depolarization distributions

This schematic presentation (based on data) presents correlation between the distribution of activation, theoretical representation of the electric field, and the surface potential distribution for 2 different instants of QRS in normal dog The torso has been bisected and the right half is shown. The heart region is indicated by the dark area The electric field lines are shown on the median sagittal surface in relationship t the instantaneous distribution of depolarization hich is spatially protected out of the plane. The field does not intersect the torso surface but is bent by the external boundary A cutaw y of the activation distribution is illustrated so that the field can be visualized in relationship to the depolarization discontinuities. The field lines iewed from body surface ould be at right angles to the equipotential lines originating from the maxima and oriented toward the minima.

1 *A* note the dipolar effect produced by the posterior opening in the cone-like configuration of excitation.
1 *B* note the nondipolar effect produced by the anterior discontinuity in the depolarization distribution resulting from epicardial breakthrough.

discontinuities in the depolarization distribution produce an electric field in the torso due to noncancellation caused by these openings. Current flows from the sources, through the openings in the depolarization distribution and toward the sinks as illustrated in Fig 11 Positive potentials are present on the torso where current flows outward from the sources and negative potentials exist where current flows away from the torso toward the sinks. Although this approximation is an oversimplified model of the electric field produced by depolarization it fits with the observed correlation between activation and surface potential data.

1 THE VCG AND VENTRICULAR ACTIVATION IN THE NORMAL DOG. In Figs. 5 and 6 the relationship between the sequence of excitation and the VCG is presented In Fig 5,*A* which correlates the epicardial activity and the VCG note that the loop begins its inferior and posterior displacement coincident with increasing breakthrough of the activation fronts at the ventral (anterior) epicardium. Note that since breakthrough occurs centrally in the anterior cardiac mass and *moves symmetrically posterior the posterior displacement in the VCG is in a* plane perpendicular to the illustration (sagittal plane) In Fig 6 which correlates the transmural activation process with the VCG it may be noted that the circumferential surface of activity about the cavity of the left ventricle at 15 msec. can be seen to form a cone open at the mitral area and closed at the apex, if one mentally connects the boundaries of activity through the 4 sections of the heart. This configuration of activation produces the anterior displacement of the VCG Subsequently with increasing breakthrough of activity in the anterior wall of the heart at 22 msec. the loop moves inferiorly and posteriorly

2. EQUIPOTENTIAL MAPS AND VENTRICULAR EXCITATION IN THE NORMAL DOG Fig 12,*A* through *D* illustrates 4 successive instances of ventricular excitation and the simultaneous distribution of body surface potential in one normal dog The heart containing the instantaneous electromotive surface is viewed through the transparent torso. The electromotive surface distribution is indicated by the positive (depolarization moving toward the observer) and negative *(depolarization moving away from the*

Fig 11 Surface isopotential distribution and the simultaneous heart generator configuration ventricular excitation in the normal dog

The configuration of current generator activity within the ventricles and the resulting surface potential distribution for 4 instants of excitation are illustrated in sequence for 7 14 22, and 32 msec. in *A B C*, and *D* respectively The isopotential maps are indicated on the dog torso surface. The boundaries of excitation are represented by the darker areas (current flows from the positive toward the negative surfaces) which are located within the ventricular walls (the lighter shaded mass) and viewed through the transparent torso. The frontal VCG is presented for time reference.

In *A* activity is present in the left septum and right ventricular free wall t 7 msec. of depolarization. I this dog, 2 potential maxima are noted on the torso t this time, in other animals, only one was noted.

I *B* there is a circumferential distribution or cone of activity in the lower positioned left ventricle and septum The pex of this "cone points toward the front surface of the torso and there is an opening in the base of the electromotive distribution which is directed toward the back of the torso (see Fig 6). Also there is a surface of excitation in the upper positioned right ventricular free wall which is confluent with the cone of activity in the left entricle and septum The visible opening in this surface of current generators represents the termination of activity pon reaching the anterior epicardium Note, that although excitation has reached the epicardium in this animal, there is but one maximum of potential on the torso surface. However there is pseudopodlike irregularity of the surface potential on the pper part of the chest which suddenly developed from a more symmetrical distribution with the occurrence of breakthrough.

In *C*, the generator configuration is considerably more complex. Note the large opening in the electromotive distribution close to the front aspect of the torso with the "rim of positivity (current sources) facing nearby points on the lateral surfaces of the torso. The ternal region of the torso "views the proximal opening in the excitation front. Current emerges from the source side (positi side) of the generators and flows outward toward the torso in these areas. Current flows aw y from the torso through the anterior discontinuity in the generator surface resulting from epicardial breakthrough.

In *D* the predominant generator activity is located near the back of the left ventricle, t the base These generators point way from the front of the torso resulting in an anterior minimum and posterior-lateral maximum. Note the irregular contour of the surface map and the nderlying regions of activity in the more closely *positioned right ventricle*

viewer) charges on the double layer and is viewed within the ventricular walls as if the heart were also transparent. The frontal plane VCG is presented for time reference. In *A* at 7 msec. initial activity can be visualized in the left septum and ventral (anterior) left ventricular free wall as well as in the right free wall endocardium. Since the excitation is moving from endocardium toward epicardium and toward the viewer the positive side of the double layers are visualized. Note that the body surface potential distribution at this instant is characterized by 2 maxima over the sternum. However frequently only one maximum was observed during this phase.

In *B* at 14 msec. of excitation, the area of activity has increased. Excitation from left and right has fused to form a common boundary in the septum and breakthrough

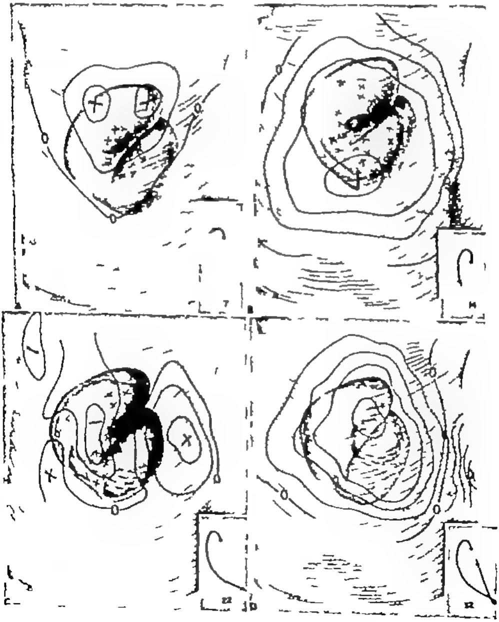

Fig. 12. For legend see opposite page.

has occurred at the anterior right ventricle causing a central opening in the electromotive surface at this point. The perimeter of the electromotive distribution in the right ventricle indicates the endocardial boundary of activation. There is a circumferential distribution of activity about the left ventricular cavity open at the inflow region dorsally (posterior) and cannot be seen from the anterior perspective (see Fig 11,A). Note the strong dipolar effect of this generator configuration in the left ventricle on the body surface potential distribution.

In *C* at 22 msec there is a wide opening in the dipole layer at the ventral (anterior) aspect of the ventricles. The central opening of this electromotive distribution represents the point at which the active surface has intersected the epicardium. Again the perimeter of this charged surface represents the boundary between the active electromotive distribution on the endocardium and polarized ventricular tissue. In between these 2 boundaries is the three dimensional surface of depolarization. As one looks through the opening resulting from epicardial breakthrough the negative or back surface of the excitation progressing away from the observer in the inferior part of the left and right free walls can be observed through the positive rim of activity at the anterior aspect of the heart. The source side (positive charges) of the generator surfaces face the sides of the torso and outward current is associated with positive body surface potentials there. The center of the torso faces the opening in the generator surface and current flowing toward the sinks away from the center of the torso results in negative potentials on the body surface at this point (see Fig 11 B). Note that a relative maximum of body surface potential (the saddle) results in double minima over the right anterior chest. This saddle or strip of relatively positive potential is related to the surface of generators in the right ventricular free wall.

In *D* at 32 msec the predominant wave fronts are located in the basal left ventricle moving away from the observer. This produces a diffuse anterior minimum.

Correlation of body surface potentials and ventricular excitation in RVH. The transmural activation studies demonstrated that there was no disturbance in the propagation of the impulse to and through the myocardium. The time of onset of endocardial activation of the right ventricular free wall was not consistent with a conduction delay or block. The activity progressed across the free wall in a manner consistent with normal conduction through a thickened ventricle. The pattern of septal activation was abnormal in the dogs with RVH due to the marked increase in septal mass. This phenomena was more obvious in the dogs with subpulmonary stenosis and intact ventricular septum.

1. VCG AND VENTRICULAR EXCITATION IN RVH. Figs. 7 through 10 illustrate the effect of ventricular activation in RVH on the VCG. In Fig 7 which demonstrates the epicardial activation in the dog with subpulmonary stenosis and intact ventricular septum note the relationship between the spatial sequence of epicardial activity depicted on the ventral (anterior) aspect of the heart and the spatial temporal characteristics of the frontal VCG. The clockwise progression of epicardial breakthrough moving from left ventricular apex to right ventricle laterally and then cranially (superiorly) correlates with the clockwise rotation with superior displacement in the VCG. The posterior superior rightward displacement of the loop beginning at 15 msec is due to the disappearance of cancelling depolarization over the anterior inferior left side of the cardiac mass. In Fig 8 demonstrating the transmural activation of the VCG in the same dog note the effect produced in the VCG by the circumferential surface of activity surrounding the ventricular cavities in the 4 sections of the heart. As in the normal dog this cone like distribution produces an anterior inferior vectorcardiographic displacement because of the opening in the electromotive activity at the heart base. With the onset of breakthrough of activity in the anterior (ventral) left ventricle the VCG moves upward and to the dog's right and posterior. The maximum superior displacement is produced by the unopposed activation fronts in the superiorly positioned right ventricle. These fronts of activity demonstrated the greatest surface area at this point in time.

In Fig 9,A which correlates the epi-

cardial activity in one of the dogs with double outlet right ventricle with the frontal VCG note that the resultant vector cardiographic displacement after 44 msec. is not directed upward toward the outflow tract, but is affected by the wide surface of wavefronts spanning the lateral margin of the right ventricle. Fig 10 represents the transmural ventricular activation and the spatial VCG as viewed frontally in this dog Again observe that circumferential activity surrounding both ventricular cavities is associated with anterior inferior vectorcardiographic displacement. The spatial orientation of this displacement correlates with the base to apex inclination of the heart. The VCG at this instant (25 msec.) is principally affected by the openings in the electromotive surface produced by the natural boundaries of the mitral and tricuspid valve areas at the base. Subsequent to the onset of epicardial breakthrough in the left ventricle, which precedes that of the right the unopposed fronts of activity in the right free wall produce rightward displacement of the vectorcardiographic loop. At 50 msec. the total surface area of the wave fronts in the right ventricle is less than at 40 msec therefore there is decreasing spatial voltage in the VCG

2. EQUIPOTENTIAL SURFACE MAPS AND VENTRICULAR EXCITATION IN RVH Fig 13,*A* through *D* illustrates four successive instants of ventricular excitation correlated with the equipotential distribution of voltage for the same instants of time. The VCG is presented for time reference. The format of presentation is the same as in Fig 12. In *A* at 24 msec. of ventricular excitation, breakthrough of activity over the ventral (anterior) and apical portions of the left ventricle results in a negative pseudopod of potential which projects upward from the left lower aspect of the torso. Note that the contour of the equipotential distribution conforms closely to the configuration of the opening in activation surface at this instant of time. The location of greatest positive potential is influenced by the closeness of the generators to the body surface at this point thus demonstrating the combined effect of generator configuration and geometry In the subsequent Fig 13 *B* through *D* there is a definite correlation between the instant to instant distribution of the body surface potentials and the generator activity Terminal activity in the outflow tract of the right ventricle is indicated in the surface map but not the VCG (Fig 13,*D*)

The time aligned sequences of surface potentials and ventricular activation in Figs. 12 and 13 illustrate a predictable relationship between the surface information and the process of ventricular depolarization. In the normal dogs, the initial epicardial breakthrough in the right ventricular free wall resulted in the rapid emergence of an anterior thoracic minimum of relatively high gradient, on the body surface overlying the opening in the electromotive surface within the heart. The subsequent surface voltage distributions produced by the progressive opening up of the electromotive surface at the epicardium permit an analysis of the sequence of epicardial excitation

The pattern of epicardial excitation and the sequence of isopotential surface maps in the dogs with RVH also demonstrate a predictable cause and effect relationship Initial epicardial breakthrough occurred over the left ventricle and subsequent activity moving left to right and clockwise produced a similar effect in the resultant body surface potential distribution Thus "inside-outside" relationship is apparent even though considerably influenced by the irregular geometry of the biologic system

Genesis of the QRS potentials of RVH Previous studies in dogs with experimentally produced right bundle branch block demonstrated a delay in septal activation.[18] The maximum spatial voltage in the VCGs of those dogs was related to septal depolarization. In these animals with RVH the maximum spatial magnitude was related to the excitation of the right ventricular free wall The basis of these large fronts was the thickened right ventricle which resulted in (*1*) A prolonged phase of right ventricular intramural depolarization with delay in epicardial breakthrough in the right ventricle and earlier breakthrough in the left ventricle (*2*) A larger instantaneous surface of excitation in the right ventricle compared to the normal dog The combination of these 2 factors resulted in large fronts of relatively unopposed activity in the hypertrophied right ventricle. This

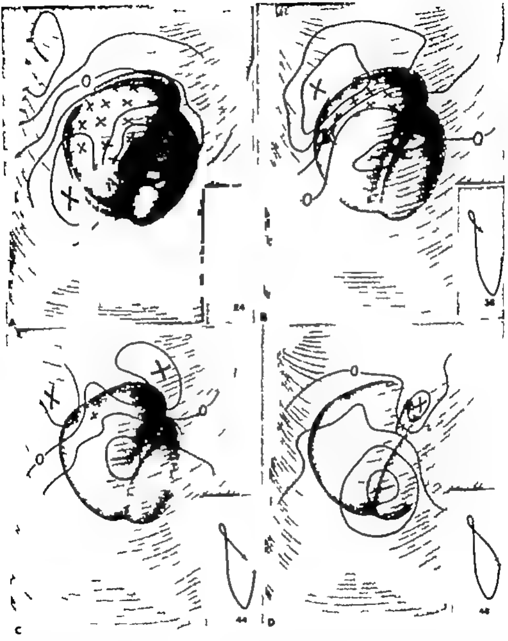

Fig. 13 Surface isopotential distribution and simultaneous heart generator configuration in the right ventricular hypertrophy dog.

The presentation is the same as in Fig. 12. Four instants of ventricular excitation at 24, 38, 44, and 48 msec. are illustrated in A, B, C, and D, respectively. In 1–4 the configuration of the boundary of epicardial breakthrough on the ventral surface of the heart produces a similar pseudodipolelike contour of surface potential. The outward moving activation front in the right ventricle terminates at the epicardium in a sequence which is reflected in the changing surface potentials. The latest area of depolarization is indicated in the pulmonary conus region and occurs after the completion of QRS in the loop. Note that although the pattern of epicardial excitation can be predicted from the sequence of surface maps it is the total distribution of depolarization which is reflected in the potentials.

distribution of activation resulted in the potential maximum over the right side of the torso and the minimum over the left during the latter part of QRS. This relationship between ventricular thickness, the total area of depolarization and the body surface potential distribution is also demonstrated by comparing the data in Figs. 12 C and 13,A. In the normal dog at 22 msec. (Fig. 12 C) the relatively small area of the activation front in the thin right ventricle produces only a relative maximum ("saddle") which separates the 2 minima. In the dog with RVH (Fig. 13,A) the broad surface of generators in the thick right ventricle results in a large region of positive potential (absolute maximum) on the torso near the right ventricle.

The effect of ventricular geometry on the pattern of excitation. This study indicates that the variations observed in the pattern of ventricular depolarization (and resulting surface potentials) in the 3 groups of dogs (i.e. normal and the 2 types of RVH) were primarily due to differences in the anatomic geometry of the ventricles. The differences between the normal and RVH dogs' ventricles do not require further emphasis. However, the more subtle differences between the 2 types of RVH should be noted since they were associated with distinctive patterns of activation and resulting surface potential distribution. By comparing the illustrations of the intact hearts in Figs. 8 and 10, certain differences in the distribution of cardiac mass can be noted. In the dogs with severe subpulmonary stenosis and intact ventricular septa (Fig. 10) there was a uniform increase in mass distributed over the entire area of the right ventricle. Thus, the relative ventricular mass in the regions of the pulmonary conus, atrioventricular margin and posterior-lateral right ventricle was similar to the normal distribution. This factor coupled with a similar sequence of endocardial excitation accounted for the similarity in the local spread of right ventricular epicardial excitation observed in these dogs and normal dogs. Comparison of Fig. 7 with Fig. 5 shows that the wavefront reached the right ventricular epicardium in the same sequence as in the normal dog. However, the onset of the earliest region of activity was delayed because of the increased thickness of the right ventricle.

In the 2 dogs with double outlet right ventricle, the relative distribution of the ventricular mass did not resemble the normal pattern. The mass was much greater along the atrioventricular margin and posterior lateral wall of the right ventricle than in the pulmonary conus region. Observe the dissimilarities in the sequence of right ventricular epicardial excitation in the 2 varieties of RVH illustrated in Figs. 7 and 9,A.

The observations that specific types of myocardial geometry are related to certain structural and hemodynamic abnormalities, and that these variations in geometry result in distinctly different patterns of excitation and body surface potentials, may be important in future clinical electrocardiography.

Relative information in surface potentials. The data obtained in this study adds to the evidence which indicates that there is considerable nonredundant or nondipolar information in the body surface isopotential maps. Also, there is information of depolarization in surface maps after the completion of QRS in standard ECG's and VCG's, Figs. 3,D and 13,D. For this reason, it is feasible to record from multiple body surface points in order to produce more information about the heart's activity and structure. The most meaningful method of comparing equipotential maps and VCG's relative to their information content is to compare them both with the known cardiac source distribution (activation). This has been done in this study and it is apparent that both methods are useful. The corrected VCG approximates an "equivalent resultant of the total activity for any one instant, whereas equipotential surface maps constructed from measurements at multiple external locations provide additional information which reflect the spatial and temporal order of local excitation. This latter type of information is useful in defining regional changes in cardiac structure.

These results demonstrate that the combined discontinuities in the distribution of depolarization correlate most closely with the distribution of surface potentials. A major discontinuity, and one that has a

large effect on the surface potential distribution as that produced by the opening in the cardiac mass at the heart base. Because of its distance from the body surface, its fixed position and relatively constant effect, this posterior opening in the generator distribution contributes a large dipolar component to the cardiac electric field (Fig. 11,*A*).

Another important discontinuity is that resulting from epicardial breakthrough. Because of the nearness of the anterior and lateral surfaces of the heart to the torso surface, the complex distribution of the electric field resulting from epicardial breakthrough in these areas produces most of the discontinuity and irregularity (nondipolarity) observed in the surface potentials, Fig. 11,*B*. This indicates that local events of the heart's depolarization can be qualitatively determined from the body surface potentials when the source-sink boundary passes through these areas. Similarly, boundaries of excitation in the posterior wall and septum, because of their distances from the torso surface, produce less obvious nondipolar (local) effects.

Summary

Equipotential surface maps were generated by digital computer technique from 200 thoracic ECG's recorded from normal dogs and 5 dogs with spontaneous RVH. Corrected VCG's were also recorded *using the axial lead system. Epicardial and trans*mural ventricular activation studies were performed in all animals and sequence maps of ventricular depolarization were produced. The mechanisms of altered QRS potentials in RVH were demonstrated by correlating the major surface and cardiac electrical events. Differences in the patterns of body surface potential distribution were related to specific variations in the distribution of ventricular mass in 2 forms of RVH. The information in equipotential surface maps and VCG's was qualitatively compared by correlating the 2 displays with the changing distribution of depolarizing wavefronts. The distribution of surface potentials and vectorcardiographic displacements were observed to be primarily influenced by discontinuities in the activation distribution. The size of these discontinuities or openings and their locations in relationship to the torso were important in determining whether surface potentials were dipolar or nondipolar. It was also observed that changing nondipolar potentials correlated with the sequence of localized depolarization of the heart, both in the normal dogs and those with RVH.

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REFERENCES

1. Durrer, D., Roos, J. P., and Büller, J.: The spread of excitation in canine and human heart, *In* Taccardi, B., and Marchetti, G., editors: Electrophysiology of the heart, Oxford, 1965, Pergamon Press, Inc., p. 203.
2. Hill, John D., and Moore, E. N.: Epicardial excitation studies in dogs with congenital right ventricular hypertrophy, Circulation Res. 20:649, 1967.
3. Boineau, J. P., Spach, M. S., and Wallace, A. G.: Ventricular excitation and body surface potentials in experimental right ventricular hypertrophy, Circulation Supplements, 1966 (Abstr.)
4. Boineau, J. P., Hill, J., Spach, M. S., and Moore, E. N.: Origin of surface potentials in right ventricular hypertrophy. To be published in the Proceedings of the Seventh Colloquium on Vectorcardiography held in Bratislava, Czechoslovakia, 1966.
5. Spach, M. S., Boineau, J. P., Barr, R. C., Wallace, A. G., Long, E. C., Gallie, T. M., and Mauney, M. F.: Isopotential surface maps in children with varying types of right ventricular hypertrophy. To be published in the Proceedings of the Seventh Colloquium on Vectorcardiography held in Bratislava, Czechoslovakia, 1966.
6. Wallace, A. G., Spach, M. S., Estes, E. H., and Boineau, J. P.: Activation of the normal and hypertrophied human right ventricle, in press.
7. Boineau, J. P., Spach, M. S., and Ayers, C. R.: Genesis of the electrocardiogram in atrial septal defect, Am. Heart J. 68:637, 1964.
8. Taccardi, B.: Distribution of the heart potentials on dog's thoracic surface, Circulation Res. 11:862, 1962.
9. Taccardi, B.: Distribution of heart potentials on thoracic surface of normal human subjects, Circulation Res. 12:341, 1963.
10. Horan, L. G., Flowers, N. C., and Brody, D. A.: Body surface potential distribution. Comparison of naturally and artificially produced signals as analyzed by digital computer, Circulation Res. 13:373, 1963.
11. Boineau, J. P., Spach, M. S., Pilkington, T. C., and Barr, R. C.: Relationship between body

surface potential and ventricular excitation, Circulation Res. 19:489, 1966.

12. Spach, M. S., Silberberg, W. P., Boineau, J. P., Barr, R. C., Long, E. C., Gallie, T. M., Gabor, J. B., and Wallace, A. G.: Body surface isopotential maps in normal children, 4 to 14 years, Am. Heart J. 72:640, 1966.
13. Neufeld, H. N., DuShane, J. W., and Edwards, J. E.: Origin of both great vessels from the right ventricle. II. With pulmonary stenosis, Circulation 23:603, 1961.
14. McFee, R., and Parungao, A.: An orthogonal lead system for clinical electrocardiography, Am. Heart J. 62:93, 1961.
15. Spach, M. S., Boineau, J. P., Long, E. C., Gabor, J. B., and Gallie, T. M.: Genesis of the vectorcardiogram (electrocardiogram) in endocardial cushion defects. Vectorcardiography 1965. Hoffman, I., and Taymor, R. C., editors, 1966, North Holland Publishing Company.
16. Veneroso, R. S., Sonnenstein, M., Stuckey, J. H., and Hoffman, B. F.: Activation of subendocardial Purkinje fibers of the left septal surface before and after left bundle branch block, Am. Heart J. 63:346, 1962.
17. Scher, A. M., and Young, A. C.: Ventricular depolarization and the genesis of QRS, Ann. New York Acad. Sci. 65:768, 1957.
18. Boineau, J. P., Spach, M. S., and Ayers, C. R.: Time normalized correlation of ventricular activation and the vectorcardiogram, Am. Heart J. 73:64, 1967.
19. Durrer, D., van der Tweel, L. H., Berreklouw, S., and van der Wey, L. P.: Spread of activation in the left ventricular wall of the dog. IV. Two and three dimensional analysis, Am. Heart J. 50:860, 1955.
20. Spach, M. S., Huang, S., and Ayers, C. R.: Electrical and anatomic study of the Purkinje system of the canine heart, Am. Heart J. 65:664, 1963.

Urokinase therapy in pulmonary thromboembolism

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Appreciation in recent years of the incidence and significance of pulmonary embolism has resulted in attention being focused on this lesion. It is the commonest form of pulmonary disease in hospitalized adults, producing approximately 2 per cent of deaths and contributing to many more.

The choice of appropriate therapy for pulmonary embolism is essentially dependent upon the magnitude of obstruction present in the pulmonary circulation. Anticoagulation to prevent recurrent emboli is essential in all patients and the only requirement in those with a minor degree of obstruction. In patients with massive embolism, when death threatens within minutes, surgical embolectomy has proved feasible and may be lifesaving.

An intermediate group of patients remains with sufficient obstruction to produce symptoms of varying degrees and the potential of delayed death or prolonged and even permanent morbidity. Such patients tolerate poorly even small recurrent emboli which represent a constant threat. In this intermediate group a means other than surgical for removing the obstruction would be desirable to eliminate the threat of death and reduce the period of morbidity.

Thrombolytic therapy theoretically represents such an approach since if effective would not only improve the hemodynamic situation but would also increase tolerance of another embolus should it occur. In addition, the likelihood of further embolization might be decreased by lysis of thrombus at the primary site. Thrombolytic therapy has been shown capable of producing dissolution of both experimental and spontaneously occurring thromboembolism in animal models and in man.[1-5] Experimental pulmonary emboli even when partially organized, as may be expected in patients, have undergone lysis with thrombolytic therapy.

Urokinase presently represents the most promising thrombolytic agent available because it is nonpyrogenic and nonantigenic and induces a predictable lytic state sufficient to achieve "therapeutic" proportions.[5,6]

Currently a cooperative randomized trial is being undertaken to evaluate the efficacy of urokinase in the therapy of patients with major pulmonary embolism.

Several groups have investigated the feasibility of using the drug in such patients and preliminary reports from these studies are beginning to appear.[7] This communication describes experience gained in patients with major pulmonary emboli

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treated with urokinase infusion at the University of Colorado Medical Center during an 18-month period.

Materials and methods

A total of 13 patients with symptoms suggestive of massive pulmonary embolism were studied. Five were considered acute in that all symptoms had developed within 14 days, with major worsening having occurred within 24 hours of thrombolytic therapy.

Four subacute patients were treated. In this group there had been clinical evidence of recurrent embolism with residual symptoms for more than 2 and less than 6 weeks prior to urokinase. All patients in this group had developed symptomatic evidence of fresh embolization within 72 hours before treatment.

Three patients had chronic symptoms thought to result from recurrent embolism for more than 6 weeks, again associated with some but not marked worsening within a week of urokinase.

One patient thought initially to have acute pulmonary embolism presented unusual findings which will be discussed separately.

In all patients with clinically suspected emboli selective pulmonary angiography was considered confirmatory and in most pulmonary isotopic scans and hemodynamic studies including pulmonary artery (PA) pressure Fick cardiac output were performed prior to urokinase therapy.

The urokinase employed was a purified preparation with specific activity of 35,000 CTA units* per milligram of protein supplied by the Committee of Thrombolytic Agents of the National Heart Institute.†

Lytic activity was achieved with a priming dose of 1 600 to 2 000 CTA units per pound given in a 10-minute period and sustained with a similar amount of urokinase each hour delivered into the central venous system through a polyethylene catheter by a continuous infusion pump.‡

The duration of thrombolytic therapy ranged from 8 to 12 hours. Plasma fibrinolytic activity was monitored serially during infusion by the euglobulin lysis and fibrin plate assays.[8] A euglobulin lysis time of 0.5 to 1.0 units and fibrin plate activity of 200 to 400 mm. were considered optimal. Also performed to determine alterations produced in the coagulation and fibrinolytic mechanism was 1-stage prothrombin and thrombin clotting time, platelet count, and fibrinogen and plasminogen levels.[9-11] In addition hematocrit, reticulocyte and serum lactic dehydrogenase (LDH) and serum glutamic oxalacetic transaminase (SGOT) values were obtained prior to and daily for 1 week following therapy. Heparin was withheld during infusion and resumed in doses sufficient to achieve anticoagulation within 6 to 8 hours after urokinase.

Following completion of urokinase therapy studies considered objective means for evaluating obstruction of the pulmonary circulation were repeated within 6 to 18 hours. These included lung scan, selective pulmonary angiogram, and hemodynamic values. Twelve hours post infusion was chosen as the optimal time for follow up studies since it was felt it represented the point at which essentially all changes induced by urokinase would have occurred and those due to spontaneous resolution were likely to be minimal.

Results

Acute patients. The 5 patients in this group ranged in age from 37 to 73 years (Table I). Each had conditions predisposing to thromboembolism, but in all, the pulmonary embolus represented the major abnormality. When admitted all patients were quite ill with fever, tachypnea, tachycardia, cyanosis and diaphoresis. Each had signs of pulmonary hypertension, 3 were in right heart failure and 1 patient was in shock. Objective studies confirmed the presence of major obstruction of the pulmonary circulation. Pulmonary angiograms revealed bilateral disease in all patients. Pulmonary artery pressure was elevated ranging from 40/26 to 70/30 mm. Hg and the average of mean pressure was 38 mm. Hg. Administration of 100 per cent oxygen for 15 minutes in

*The CTA (Committee on Thrombolytic Agents) units is the standard urokinase unit of activity established by the Committee on Thrombolytic Agents of the National Heart Institute.

†Manufactured by Abbott Laboratories, Chicago, Ill., and Sterling-Winthrop Laboratories, Rensselaer, N. Y.

‡Harvard Instrument Company, Boston, Mass.

Table I. Urokinase therapy in pulmonary embolism. Acute symptoms (<14 days)

Patient	Age	Associated lesion	Symptoms: Duration (days)	Symptoms: Severity (1-4)	Lytic state (1-4)	Result: Clinical	Result: Angiographic
1 R B	37	Phlebitis	1	3+	2+	2+	4+
2 C Y	39	Brain tumor, phlebitis	4	2+	1+	2+	2+
3 J H	39	Phlebitis	14	3+	3+	3+	3+
4 A M	59	Cirrhosis	7	4+	1+	3+	2+
5 C W	71	Cerebrovascular accident	10	4+	3+	4+	3+

Table II. Urokinase therapy in pulmonary embolism. Subacute symptoms (2-6 weeks)

Patient	Age	Associated lesion	Symptoms: Duration (wk)	Symptoms: Severity (1-4)	Lytic state (1-4)	Result: Clinical	Result: Angiographic
6 J W	53	Obesity	4-6	2+	1+	1+	1+
7 J D	67	Atherosclerosis amputation	6+	+	1+	2+	2+
8 O H	70	Cancer of the breast	2-3	4+	1+	3+	1+
9 M K	70	Prostatism	4-6	2+	1+	1+	1+

several patients resulted in no significant decrease of mean PA pressure. This suggested that pulmonary hypertension resulted from mechanical obstruction rather than vasoconstriction. Arterial saturation ranged from 83 to 90 per cent, with an average pO_2 of 50 mm.

The lytic state achieved with urokinase infusion was considered optimal in 3 and less than optimal in 2 of the patients. All patients in this group had clinical improvement during the thrombolytic therapy. In the 2 most severely ill patients this was dramatic. Initially it appeared that both patients might have a fatal outcome, but after a few hours of urokinase they had stabilized and survival seemed assured. The 3 other patients were less severe when initially seen, but had appreciable relief of respiratory symptoms during treatment.

All patients in this group demonstrated major improvement in follow-up angiograms (Fig. 1,*A*, *B*, and *C*). In none did it appear that all embolic material had lysed at the time of the postinfusion study, but sufficient had occurred to result in major improvement of pulmonary perfusion. The PA pressure fell in each patient (Fig. 2) associated with a stable or increased cardiac output. This indicated reduction in pulmonary resistance had occurred, presumably due to removal of obstructing thrombus. Arterial pO_2 increased in all patients, with average pO_2 rising to 62 mm., but reached normal levels in only Patient 3.

Serial lung scans returned to normal in each patient during follow-up, and all symptoms and signs of pulmonary hypertension cleared.

Subacute patients. Of the 4 patients with subacute symptoms, 3 were moderately and 1 severely ill at the time of treatment (Table II). Each had symptoms resulting from prior emboli for 2 to 6 weeks antedating the episode which finally brought them to attention. Cardiac catheterization demonstrated pulmonary hypertension in

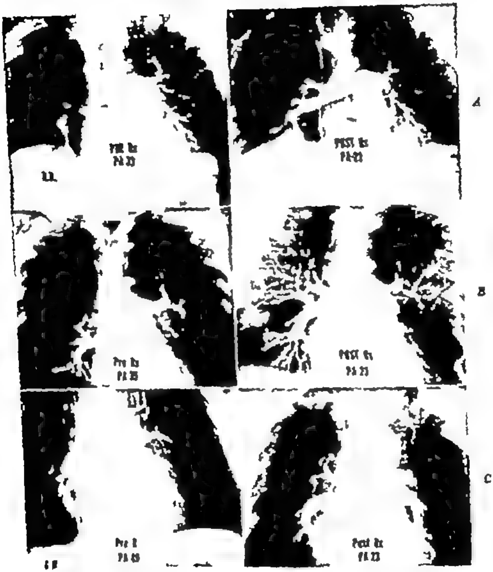

Fig. 1. *A*, Patient 1, left panel pre Rx, there is major occlusion of main right pulmonary artery resulting in hyperperfusion of the left lung and virtually no flow to the right. PA pressure 52/24 (mean 33); right panel post Rx, 12 hours after urokinase, no embolus is apparent in the right pulmonary artery and pressure had decreased to 39/15 (mean 23). Flow to the right lung is less than the left suggesting some obstruction remains. *B*, Patient 3, left panel, filling defects are present in the main right pulmonary artery and all lobar branches and flow to that side is markedly decreased. There is no flow to the left lower lung. PA pressure 50/28 (mean 35); right panel, the embolus in the right side of the pulmonary arterial tree is gone and marked increase of flow to that side has occurred. Left lower lung now is also being perfused. Branch to apex of left lung shows persistent involvement. PA pressure 37/18 (mean 23) with increase of cardiac index from 2.4 to 2.9 L. per minute per square meter. *C*, Patient 5, left panel, practically complete obstruction of the main right and left lower lobe arteries in this patient in severe distress with acute cor pulmonale; right panel, 12 hours after urokinase, there is flow to entire right and left lower lung. The patient was comfortable and all signs of pulmonary hypertension had cleared. Pulmonary pressure had decreased from 60/22 (mean 40) to 38/16 (mean 23).

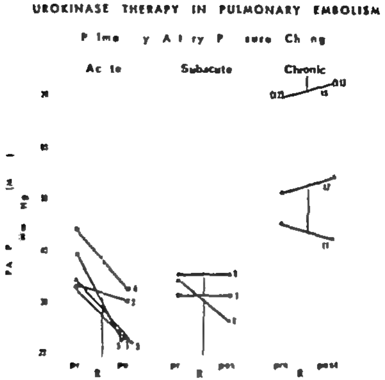

Fig. 2. Mean PA pressure before and after urokinase therapy in patients with acute (2 wk.), subacute (6 wk.), and chronic (>6 wk.) symptoms. Numbers identify patients as on Tables.

the same range as in those with acute symptoms. Angiograms revealed major pulmonary obstruction but it was not possible to distinguish recent from older lesions.

The intensity of lytic activity produced was suboptimal in 3 and excessive in 1 patient. The latter patient was extremely obese and dose calculated on body weight might be expected to prove excessive.

Symptomatic improvement occurred in all patients during infusion but was dramatic only in the severely ill one. In that case stabilization resulted after several hours of treatment. Physical findings in all patients following therapy continued to suggest the presence of pulmonary hypertension and dyspneic symptoms improved only gradually.

Pulmonary pressure remained elevated in this group of patients with a decrease observed in just 1 case (Fig. 2). Pulmonary angiograms demonstrated minor improvement in each patient, but in none was there evidence of major change. When pleuritic pain suggested the location of recent embolism that area often revealed the most evidence of revascularization. Significant discrepancy between angiogram and lung scan occurred in 1 patient (Fig. 3). Here slight improvement was suggested by angiogram but much less than shown by lung scan. The inference of this would seem to be that significant improvement in regional perfusion is possible without requiring complete removal of obstructing lesions.

Catheterizations were not repeated beyond the immediate posttreatment period so that a definite statement concerning the rate of normalization is not possible. However all patients gradually became asymptomatic and lung scans returned to normal. An important point was demonstrated by the patient severely ill prior to therapy. Following urokinase the evidence for pulmonary hypertension gradually lessened during several weeks. Three months after treatment she died of a cerebral hemorrhage. At postmortem examination, no evidence of pulmonary embolism could be found in the pulmonary circulation.

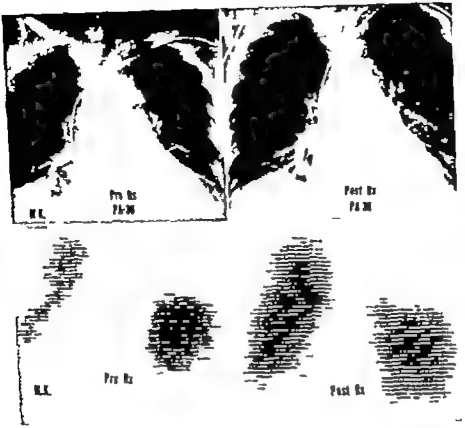

Fig. 3. Patient 9 with subacute symptoms followed by several days of increased dyspnea and right pleuritic pain. *A*, Angiograms revealed slight but not impressive improvement of blood flow to both lungs after thrombolytic therapy. PA pressure was unchanged. *B*, Posterior lung scans corresponding in time to angiogram show striking increase of regional perfusion to the right side.

Table III. Urokinase therapy in pulmonary embolism. Chronic symptoms (>6 wks.)

Patient	Age	Associated lesion	Symptoms		Lysis state (1-4)	Result	
			Duration (mo.)	Severity (1-4)		Clinical	Angiographic
10. W.R.	36	Phlebitis, schizophrenia	6+	2+	2+	0	0
11. D.H.	56	Obesity, phlebitis	2+	2+	2+	0	0
12. B.A.	72	Prostatitis	1 2	3+	2+	[illegible]	0

either by Schlesinger mass injection or careful dissection. It appears that while most lyseable embolus may be rapidly removed during urokinase therapy, some remains which gradually disappears, presumably also by lysis. It is supposed that the length of time embolic material is in the pulmonary circulation alters significantly the urokinase effect, since endothelialization which occurs within a few days would influence the amount of fibrin exposed to the enzymatic activity.

Chronic patients. The 3 patients in this group were all in heart failure when seen associated with physical findings, ECG and catheterization abnormalities which suggested the etiology to be chronic cor pulmonale secondary to obliterative pulmonary hypertension (Table III). Worsening within 1 to 2 weeks of therapy suggested that recent, probably minor embolization had occurred.

Therapeutic levels of lytic activity were achieved in each case; however, no major symptomatic improvement or change in physical signs was appreciated during urokinase. Catheterization and angiography following treatment failed to demonstrate significant change (Fig. 2).

All patients gradually improved clinically with vigorous cardiac therapy but persisted with evidence of severe pulmonary hypertension confirmed in by repeat catheterization after 4 and 6 months. Serial lung scans from a patient in this group exemplify the persistence of perfusion abnormality over a 4 month period. Angiogram in that patient revealed marked *attenuation of vessels to all areas of lung* and apparent obstruction to the left upper lobe vessel (Fig. 4,*A* and *B*).

One additional patient is deserving of special comment. He presented with known chronic obstructive pulmonary disease associated with worsening of cough and dyspnea over a 4- to 6-week period. The diagnosis of acute bronchitis was made and the patient appeared to respond to therapy intended for that condition. On the fifth hospital day, he developed fever, tachypnea, anxiety, and cyanosis followed after 6 hours by right-sided pleuritic chest pain, tachycardia, and shock. Massive pulmonary embolus was suspected and thought confirmed by pulmonary angiography (Fig. 5). Urokinase therapy was begun and continued until he died 13 hours later. At postmortem examination an embolus was found obstructing completely the right main pulmonary artery as suspected. However, it was heavily organized and densely adherent over its

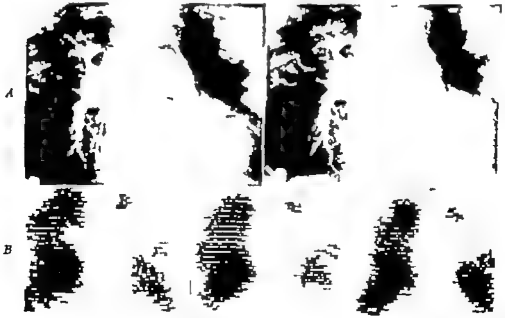

Fig. 4. Patient 10, symptoms persistent for 6 months followed by worsening and development of heart failure 1 to 2 weeks prior to urokinase. Pulmonary pressure 120/62 (mean 82). *A*, Angiograms demonstrate peripheral narrowing to all vessels and poor perfusion of right lower and left upper lung fields. *B*, Lung scans before (left panel) and 12 hours after urokinase (center) demonstrate multiple cold areas with no apparent change. Four months later (right panel), the lung scan remained essentially unchanged and the pulmonary artery pressure was 120/70 (mean 85).

full length to the wall of the pulmonary artery suggesting that it had been in that location for many days and probably weeks. No other emboli were revealed by careful dissection. This case demonstrated impressively the futility encountered when attempting to predict the composition of an obstructing lesion in the pulmonary circulation or how long it has been there and thus the likelihood that it would be lysed.

Evaluation of lytic activity. Alterations produced in assays performed are listed in Table IV. With the dose schedule employed therapeutic levels were achieved in 10 patients, although in 4 of these it would be considered suboptimal and in 1 patient excessive. Interestingly, each of the 3 patients failing to have an adequate lytic state produced demonstrated both subjective and objective improvement during therapy which in 2 cases was of marked degree.

The decrease in fibrinogen level paralleled the intensity of lytic activity and in patients with a "therapeutic" state ranged from 30 to 60 per cent. As expected, prolongation of the coagulation tests correlated with the magnitude of change in fibrinogen since they reflect the effects of breakdown products of fibrin and fibrinogen. In this small series, it appeared that "significant" change in coagulation studies was usually associated with reduction of fibrinogen by more than 33 per cent of baseline levels.

Fig. 5. Patient 13. Venous angiogram in patient with acute symptoms being treated for worsening of chronic bronchitis. Complete obstruction of right pulmonary artery found at postmortem resulted from old organized, firmly adherent embolus.

Plasminogen levels declined markedly in all patients including those with suboptimal activity. The intensity of the lytic activity influenced the rate of fall of plasminogen and to a lesser degree, the final level.

Complications. Bleeding represented the only complication encountered. There were no instances of febrile or hypotensive reactions attributable to urokinase administration. It was frequent to observe gradual decline in hematocrit to levels 10 to 15 points below baseline by the fourth or fifth postinfusion day. Significant bleeding occurred in 7 patients. In 6 this was into areas of trauma such as the arm used for catheterization, shoulder used for subclavian vein puncture, or overlying an artery from which samples for blood gases had been drawn. One patient, however, developed retroperitoneal bleeding on the day following urokinase, recognized by symptoms of flank pain, shift of ureter position on intravenous pyelogram, and delayed appearance of a Grey Turner's sign. One patient required 3 units of blood to stabilize his condition on the night of treatment following bleeding into the shoulder from a traumatized subclavian vein. The same patient had a platelet fall from 185,000 to 35,000 between the fifth and tenth postinfusion day, which gradually normalized over a 2 week period. The precise etiology of the thrombocytopenia is not clear, but because of its delayed appearance and the fact that it has not been previously reported after urokinase and that he was on other drugs, led us to discount that it was caused by urokinase.

Discussion

It would appear from this and similar studies that the dissolution rate of emboli in the pulmonary circulation may be markedly accelerated by urokinase therapy. The response is most dramatic in cases treated within several days after the embolic episode while the embolus is "fresh" and before adherence to the vessel wall and surface endothelialization occur.

Table IV. Urokinase therapy in pulmonary embolism. Biochemical alterations

Patient	Lytic activity: Euglobulin lysis time (min)	Lytic activity: FSA post Rx (mm²)	Fibrinogen (mg%): Pre Rx	Fibrinogen (mg%): Post Rx	Fibrinogen (mg%): % Fall	Plasminogen (u/ml): Pre Rx	Plasminogen (u/ml): Post Rx	Plasminogen (u/ml): % Fall	Prothrombin time (sec): Pre Rx	Prothrombin time (sec): Post Rx	Thrombin clotting time (sec): Pre Rx	Thrombin clotting time (sec): Post Rx
1 R B	0.8	305	530	325	39	4.5	1.0	78	13	17	8	14
2 C V	0.3		491	292	40	7	0.9	65	15	18	8	13
3 J H	> 1.0	410	705	287	59	4.8	1.0	80	17	23	1	25
4 A M	< 0.3	65	700	7.5	9	2.1	0.7	66	19	17	13	11
5 G W	1.0	460	350	700	33	3.6	1.0	71	15	17	10	30
6 I W	> 1.0	1,000	650	265	59	6.0	1.1	82	15	26	13	38
7 J D	0.5	700	60	730	4	3.1	0.5	84	13	14	10	12
8 O H	< 0.2	150	5.5	500	3	2.3	0.3	87	17	20	11	11
9 M K	0.5	—	692	6.4	3	2.9	1.4	52	13	14	10	10
10 W R	0.5	200	413	470	6	1.4	0.3	8	16	16	15	17
11 D H	0.7	150	800	310	58	4.6	1.5	68	15	17	15	20
12 B A	0.5	169	428	300	30	3.0	0.6	80	15	18	10	16

*1,600 to 2,000 CTA units per pound body weight for 8–12 hours.

Presumably this reflects the decreasing sensitivity to lysis that results with organization, although partially organized emboli have been shown experimentally to undergo lysis.

Emboli in the lungs which are not lysed become adherent to the vessel wall and the surface endothelialized. At that point the creation of a lytic state is unlikely to result in decreased obstruction. It is likely that in patients with subacute symptoms followed by an acute episode only the fresh material is lysed. The patient is thus returned to a clinical state similar to that existing prior to the last embolization. Such patients may have considerable symptomatic change with much less impressive improvement in objective parameters such as angiogram, lung scan and hemodynamic values. This sequence would explain the observations made in subacute patients in this series.

In chronic patients with severe fixed pulmonary hypertension it is impossible to determine the amount of fresh embolus present at the time of an acute episode. Certainly most areas of abnormality on angiogram and lung scan are likely to be due to old lesions. The fragility of such patients makes it likely that fresh symptoms result from small emboli since they would probably not survive a large one. Even if the small embolus is removed either spontaneously, surgically, or with thrombolytic therapy, there may be no significant change in objective studies and symptoms due to cardiac decompensation may be slow to improve. Results of thrombolytic therapy may thus be impossible to assess in such patients.

Series such as this establish the feasibility of employing thrombolytic therapy with urokinase in patients with major pulmonary embolism. They do not allow decision concerning the efficacy of such therapy compared to the conventional management of heparin anticoagulation and supportive care. Obviously this important question can only be answered by rigidly controlled randomized trial utilizing objective methods of evaluation.

A cooperative study with this objective is currently being planned and will soon begin.

Summary

Thirteen patients with angiographically confirmed pulmonary thromboembolism received thrombolytic therapy with urokinase for 8 to 12 hours. Cardiac catheterization, lung scan and angiograms prior to

and within 6 to 18 hours after completion of therapy were used to assess results.

Five patients with acute symptoms had marked improvement in clinical and laboratory parameters. Of 4 patients with subacute symptoms, all had clinical improvement but objective studies were less changed than in the acute group. Three chronic patients were treated and failed to demonstrate significant change in any parameter. One patient with acute symptoms died and was found to have only old organized adherent emboli pointing out the difficulty in predicting the characteristics of emboli by presently available methods.

The lytic state was tolerated well by even severely ill patients and bleeding into soft tissue represented the only recognized complication. Further controlled observations of this form of therapy are considered justified in patients with acute massive pulmonary embolism.

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REFERENCES

1. Johnson, A. J., and McCarty, W. R.: The lysis of artificially induced intravascular clots in man by intravenous injection of streptokinase, J. Clin. Invest. 38: 1627, 1959.
2. Hume, M.: Lysis of the experimental radioactive pulmonary emboli induced by streptokinase and SK-activated plasmin, Thromb. Diath. Haemorrh. 11: 99, 1964.
3. Browse, N. L., and James, D. C. O.: Streptokinase and pulmonary embolism, Lancet 2: 1039, 1964.
4. Genton, E., and Wolf, P. S.: Experimental pulmonary embolism. Effects of urokinase therapy on organizing thrombi, J. Lab. & Clin. Med. 70: 311, 1967.
5. Fletcher, A. P., Alkjaersig, N., Sherry, S., Genton, E., Hirsh, J., and Bachmann, F.: The development of urokinase as a thrombolytic agent, J. Lab. & Clin. Med. 65: 713, 1965.
6. Genton, E., and Claman, H. N.: Urokinase antigenicity in man, Clin. Res. 14: 435, 1966 (abstr.).
7. Sautter, R. D., Dean, E., Fletcher, F. W., Wenzel, F. J., and Matson, J.: Urokinase for the treatment of acute pulmonary thromboembolism, J.A.M.A. 202: 251, 1967.
8. Sherry, S., Lindemeyer, R. I., Fletcher, A. P., and Alkjaersig, N.: Enhanced fibrinolytic activity in man, J. Clin. Invest. 38: 810, 1959.
9. Alkjaersig, N., Fletcher, A. P., and Sherry, S.: Σ-Aminocaproic acid: An inhibitor of plasminogen activation, J. Biol. Chem. 234: 832, 1959.
10. Alkjaersig, N., Fletcher, A. P., and Sherry, S.: The mechanism of clot dissolution by plasmin, J. Clin. Invest. 38: 1086, 1959.
11. Ratnoff, O. D., and Menzie, C.: New method for the determination of fibrinogen in small samples of plasma, J. Lab. & Clin. Med. 37: 316, 1951.
12. Fletcher, A. P., Alkjaersig, N., and Sherry, S.: The maintenance of a sustained thrombolytic state in man. I. Induction and effects, J. Clin. Invest. 38: 1096, 1959.

The evolution of pulmonary arterial stenosis associated with congenital rubella

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After the 1964 rubella epidemic in the United States of America many infants were seen with evidence of congenital cardiovascular disorder. The most frequent lesions identified at detailed study were pulmonary arterial stenosis (PAS) and patent ductus arteriosus (PDA). PDA has long been recognized as a common sequel of first trimester infection with the rubella virus but PAS is a more recently appreciated component of the congenital rubella syndrome. In addition to the fact that relatively little has been written about PAS in older patients,[a] knowledge concerning the early development of the vascular disorder is not at all clear.

This report describes the angiographic appearances as well as the pressure differences encountered in the elastic pulmonary arteries of infants with PAS studied at the Johns Hopkins Hospital following the 1964 rubella epidemic. Correlation of this material with the age of the child during the first year of life indicates that there is a fairly constant sequence of anatomic change in the pulmonary artery branches even though the pressure in the pulmonary arteries remains fairly constant during this time period.

Material and methods

A total of 20 infants with the congenital rubella syndrome between 4 weeks and 18 months of age constitutes the patient series. All but one of the babies was under the age of 12 months when first studied. In 14 of the 20 infants rubella virus was recovered from throat or urine culture or both. In 4 others, 3 of whom were 11 months of age or more, diagnostic confirmation was obtained by serological methods. In the remaining patients, laboratory confirmation is pending but the clinical picture in both is strongly supportive of rubella infection.

The patients fall into 4 main groups.

GROUP I—Those having PDA under the age of 1 year: (a) with PAS (2 studies) and (b) without PAS (3 studies).

GROUP II—Those having PAS under the age of 6 months (4 studies).

GROUP III—Those having PAS, aged 6 months or more (7 studies).

GROUP IV—Serial studies of patients

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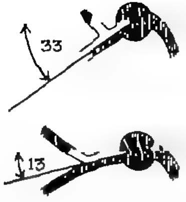

Fig. 1. Angle of intersect between the main pulmonary artery and the right pulmonary artery branch.

having PAS, (a) under 6 months of age (4 studies) and (b) over 6 months of age (4 studies).

Pressures in the trunk of the main pulmonary artery and in the right and left main branches were measured using end occluded side hole catheters of the No. 4 or No. 5 French size of the Elecath type. On occasion the Rodrigues Alvarez type catheter was used. These catheters were connected to Statham P23DB strain gauges which were calibrated against a mercury column at each study. The pressures were recorded through an Electronics for Medicine system. Zero levels in each instance were at the mid-chest. All angiographic observations were made from 35 mm. cine films taken in the antero-posterior projection following contrast injection into the main pulmonary artery. The angle of intersect was determined by measuring that angle occurring between a horizontal line drawn through the center of the main pulmonary artery and a line drawn along the axis of the right pulmonary artery (Fig. 1).

Results

Pressure measurements in the main pulmonary artery were recorded in all patients. Pressures in the branch pulmonary arteries were obtained in all but 2 instances. Peak systolic pressure differences across the bifurcation of the main pulmonary artery are tabulated below (Table I).

Group I—PDA with and without PAS under 1 months of age. The 5 patients were aged between the neonatal period and 11 months and all had definite evidence of a patent ductus arteriosus recognized by the following criteria: (1) the presence of a continuous or abbreviated duct murmur,[11] (2) demonstration of an unequivocal rise in blood oxygen saturation in the pulmonary artery over samples obtained in the right ventricle and (3) by passage of the catheter from the pulmonary artery into the descending aorta through the ductus arteriosus itself.

WITH PAS. In 2 of these patients, it was possible to enter the peripheral pulmonary artery branches. The peak systolic pressure difference between the main trunk pressure and the pulmonary artery branch pressure was 24 and 34 mm. Hg respectively. At pulmonary angiography each of these patients demonstrated an unmistakable area of narrowing at the origin of the pulmonary artery main divisions followed by some degree of post stenotic dilatation distally. The angle of intersect was under 10 degrees in both cases (Fig. 2).

WITHOUT PAS. Of the remaining 3 infants, entry into a pulmonary artery branch was achieved in only 1 and in this patient the systolic pressure difference was inconsistent varying between 0 and 23 mm. Hg. PAS was considered unlikely in these patients because pressure tracings in the main pulmonary artery failed to demonstrate a low dicrotic notch, a characteristic finding in patients with bilateral PAS.[12] At pulmonary angiography these patients having PDA without PAS had recognizable differences from those with an associated PAS, namely the main pulmonary artery was dilated and the pulmonary artery main divisions were of large size throughout without proximal constrictions. The angles of intersect in these cases were approximately 40 degrees (Fig. 3).

Group II—PAS under the age of 6 months. Four patients in this category were shown to have no ductus arteriosus by both oxygen sampling and angiographic techniques. Two were 5 months of age and the others were younger. The systolic pressure differences between the main trunk of the pulmonary artery and pulmonary artery branch averaged 20 mm. Hg and in all

Table I P essu e measu ements obtained in the pulmonary arteries of infants with congenital rubella

G oup	I ag os	C	Age (m)	MP t pres	B nch pres e	S stolic pres d ference
I	PDA (I tie t under 12 month of ge)					
A	W th PAS	764	1	59/35		
	W th PAS	901	11	77/45	31 11	24
B	W thout PAS	606	1	86/41	43/40	34
	W thout PAS	602	1	61 37	63-86 41	0-23
	W thout PAS	696		83/4		
II	PAS (I tient under 6 month of ge	519	1	50/16	30 12	20
		626	2 ?	46 11	23/9	‑3
		650	5	3? 1	20 10	16
		678	5	55 15	14 10	21
III	PAS (I tie t over 6 m nth of ge)	06	6	2 5	16 5	6
		748	6	46-56 15	2 31/8	24
		750	6	23 8	18 8	5
		767	6	30 5	13/6	36
		919	11	18/8	13 3	5
		922	11	31 8	16 8	15
		1 157	18	1 14	9 3	11
IV	PAS Serial tudies					
A	(Patients under 6 month of ge)	599A	1	35 13	23 13	12
		600A	1	36 9	15/9	1
		695A	1½	25 8	18 8	7
		568A		41 7	15/7	26
B	(I tient over 6 months of age)	599B	13	55 7	12/5	43
		600B	11	‑5 8	14/8	11
		695B	12	40 10	20/12	20
		568B	15	41 7	15/7	26

PDA, Patent ductus arteriosus PAS pulmonary artery stenosis, MPA, mai pulmonary artery

cases there was main pulmonary artery hypertension The arteriographic appearances in the pulmonary circuit were identical Each patient demonstrated a moderate sized main pulmonary artery and relatively long hypoplastic appearing main pulmonary arterial branches Furthermore no regions of constriction or post stenotic dilatation could be identified The angle of intersect between the main pulmonary artery and the right pulmonary artery was about 20 degrees in 2 cases and less than 20 degrees in the other 2 (Fig 4)

Group III—PAS age 6 months or more Seven patients with PAS without PDA were studied the oldest case being catheterized at 18 months of age The main pulmonary artery pressure was elevated in only ? instances The systolic pressure differences between the main trunk and pulmonary artery branches averaged 13 mm Hg The pulmonary arteriograms of each patient demonstrated a rather large main pulmonary artery with a proximal narrowing of the initial portion of the right major pulmonary artery division followed by dilatation of the artery This dilatation was sometimes evident distally into the lobar branches. The angle of intersect between the main pulmonary artery and the pulmonary artery branches was 20 degrees in one instance and less than 20 degrees in all others (Fig 5)

Group IV—PAS without PDA Four patients were studied serially once under 6 months of age and once beyond 6 months.

Fig. 2. Group IA pulmonary arteriogram of an individual having PDA and PAS at 1 month of age. Note the moderately sized main pulmonary artery, the proximal constriction of the branch pulmonary arteries, the distal arterial dilatation, and the angle of intersect of less than 10 degrees.

Fig. 3. Group IB pulmonary arteriogram of an individual having isolated PDA at 4 months of age. Note the dilated main pulmonary arteries, the lack of proximal constriction of the branch pulmonary arteries, the lack of distal arterial dilatation, and the angle of intersect of 40 degrees.

Fig. 4. Group II pulmonary arteriogram of an individual having PAS under 6 months of age. Note the moderately sized main pulmonary artery, the long hypoplastic branch pulmonary arteries, the lack of proximal constriction of branch arteries, the lack of distal dilatation, and the angle of intersect of less than 10 degrees.

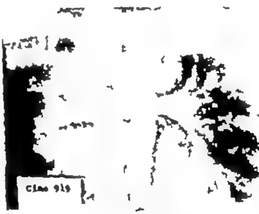

Fig. 5. Group III pulmonary arteriogram of an individual having isolated PAS over 6 months of age. Note the dilated main pulmonary artery, the marked constriction of the branch pulmonary artery segments, the pronounced distal arterial dilatation, and the angle of intersect of less than 10 degrees.

INITIAL STUDY UNDER 6 MONTHS OF AGE. Four patients were studied during the first 2 months of life. The main pulmonary artery pressure in 3 instances was slightly elevated but in the other was within normal range. The systolic pressure differences between the main trunk of the pulmonary artery and a main division of the pulmonary artery averaged 16 mm. Hg. The arteriographic appearances in all cases were similar to those described for patients in Group II with a moderate sized main pulmonary artery, hypoplastic appearing main pulmonary artery divisions, and no evidence of peripheral dilatation. The angle of intersect between the main pulmonary artery and the right pulmonary artery was less than 15 degrees in each instance (Fig. 6).

FINAL STUDY OVER 6 MONTHS OF AGE.

Fig 6 Group IV A pulmonary arteriogram of individuals having isolated PAS studied serially. First study under 6 months of age. Note the moderately dilated main pulmonary artery, the long hypoplastic branch pulmonary arteries, the lack of proximal constriction of branch arteries, the lack of distal dilatation and the angle of intersect of less than 20 degrees.

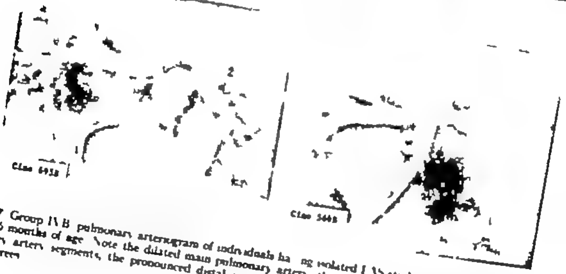

Fig 7 Group IV B pulmonary arteriogram of individuals having isolated PAS studied serially. Second study over 6 months of age. Note the dilated main pulmonary artery, the marked constriction of the branch pulmonary artery segments, the pronounced distal arterial dilatation and the angle of intersect of less than 10 degrees.

Studies were repeated in these 4 patients when they were between 11 and 15 months old. The main pulmonary artery pressures had increased moderately in 2 instances, were distinctly lower in 1 instance, and were unchanged in another case. In only 1 patient did the branch pressure fall to a lower level. The average systolic pressure difference between the main trunk and the pulmonary artery division was now 25 mm Hg. The arteriographic appearances were now similar to those described for patients in Group III where a moderately large dilated main pulmonary artery gave rise to a short narrow segment at the origin of the main pulmonary artery divisions. There was also a degree of dilatation for the remaining portion of the pulmonary artery branches. The angle of intersect between the main pulmonary artery and the right branch remained less than 20 degrees (Fig 7).

Discussion

Patients having PAS without IDA studied both individually and serially

during the first year of life demonstrated variable systolic pressure differences between the main pulmonary artery and its major bifurcations. More striking differences are apparent on analysis of the arteriograms. In the affected infant under 6 months of age, the pulmonary arteriogram shows a long hypoplastic branch without dilatation providing the PAS is not accompanied by a major left to right shunt. Should there be an associated PDA with a left to right shunt causing an increase in pulmonary blood flow, the arteriographic appearance is similar to that seen in infants over the age of 6 months who have uncomplicated PAS. This raises the possibility that the natural pattern of PAS is one of initial hypoplasia of the branch pulmonary arteries and that it is only after a period of 6 months that the more characteristic angiographic appearances of the established disorder become apparent. The fact that the process can be hastened by the addition of a left to right shunt through a PDA suggests that where PDA is not present the changes are due to a gradual increase in pulmonary blood flow with growth of the body. Serial studies during the first 18 months of life in individuals with PAS support the natural history inferred from the results of random studies in individual patients in Groups II and III. It would seem that uncomplicated PAS is not angiographically unequivocal until after the fifth month of life.

There is a limited amount of autopsy evidence to show that patients under 6 months of life with the "hypoplastic" appearances of the main pulmonary artery division, do not show abnormal histological appearances when the bifurcation zone of the pulmonary arteries is examined at section. By contrast, in patients coming to autopsy with arteriograms showing bifurcation narrowing and dilatation of distal pulmonary arteries, there is always marked intimal proliferation with some disruption of underlying elastic tissue at microscopy. While the possible role of continuing viral damage postnatally cannot be excluded as a possible explanation for the changes, it would seem more likely that an earlier and more subtle change in the matrix of the pulmonary artery wall has occurred prenatally and that the subsequent changes during the first year are the response of the weakened artery to the acceptance of the increment of pulmonary blood flow which follows birth. The site of maximal disturbance almost uniformly appears at the first point of branching in the pulmonary artery though subsequently other bifurcation zones within the arterial circuit are affected. Such points in any circuit are known to be areas where maximum turbulence occurs and where the greatest stress is placed on the vessel wall. This explanation would also account for the acceleration of changes in PAS seen in patients with an associated large PDA.

Although the findings of pressure and arteriographic differences in patients with PAS without PDA in the first 6 months of life strongly suggest abnormal smallness of the pulmonary artery divisions, there has been only limited opportunity to make comparisons of these findings with completely normal individuals of that age. It is appreciated that the pulmonary artery branches in late fetal life and in the immediate newborn period are considerably smaller than the main trunk and that it takes several months before the major pulmonary artery divisions assume their larger more mature size.[14]

The finding at cardiac catheterization of systolic pressure differences between the main pulmonary artery and its branches in apparently normal individuals have led some workers[1] to the view that the normal "hypoplasia" of the pulmonary artery branches in the young infant may be indistinguishable from the results in studies on babies with congenital rubella and that in fact such pressure differences will frequently disappear with growth after birth. Angiographic observations are even more scanty in this regard but our own limited experience suggests that while the pulmonary artery branches are small in comparison with the main trunk during the first few months of life, the taper of the right pulmonary artery from its bifurcation to a more distal portion is gradual and that the angle of intersect between the main trunk and the right branch is well in excess of 0 degrees. It is possible that exceptions to this generalization may occur where relatively "hypoplastic" pulmonary ar-

teriograms may ultimately reach a normal appearance and it could be argued that in such cases a structural alteration in the matrix of the pulmonary artery branch antenatally was so minimal that grossly normal responses to increasing pulmonary blood flow could be achieved during the first year.

Summary

The pressure relationships in the main pulmonary arteries and the pulmonary arteriograms in 20 patients under the age of 2 years with pulmonary arterial stenosis secondary to congenital rubella have been described. Systolic pressure differences between the main pulmonary artery and a major division are variable at all stages of the disorder and do not appear to progress rapidly during infancy.

Pulmonary arteriograms show that classical pulmonary artery bifurcation stenosis with post stenotic dilatation is not evident until 6 months of age unless a complicating factor of increased pulmonary blood flow as through a patent ductus arteriosus is also present. The angiographic appearance of PAS in patients under 6 months of age is demonstrated by a long hypoplastic appearance of the major pulmonary artery divisions which have an angle of intersect with the main pulmonary artery of less than 20 degrees. There is no area of visible stenosis in the proximal branch of the pulmonary arteries and certainly no recognizable degree of peripheral dilatation.

In patients with PAS under 6 months of age, however, in whom there is the complicating factor of a left to right shunt through a PDA, the angiographic appearance is similar to that seen in uncomplicated PAS in older infants. The arteriograms in both show a short stenotic segment at the origin of the right or left pulmonary artery main division and a distal dilatation of the peripheral vessels. Furthermore, the angles of intersect are under 20 degrees in both situations.

It is suggested that the changes in angiographic appearance are due to increasing stresses during the first year of life at points of branching in the pulmonary arteries. These stresses may be produced by a gradual increase in pulmonary blood flow occurring in a prenatally weakened arterial wall.

REFERENCES

1. Rowe, R. D.: Cardiovascular lesion in rubella, J. Pediat. 68:117, 1966.
2. Gregg, N. M.: Congenital cataract following German measles in the mother, Tr. Ophth. Soc. Australia 3:35, 1941.
3. Rowe, R. D.: Maternal rubella and pulmonary artery stenosis. Report of eleven cases, Pediatrics 32:180, 1963.
4. Emmanouilides, G. C., Linde, L. M., and Crittenden, I. H.: Pulmonary artery stenosis associated with ductus arteriosus following maternal rubella, Circulation 29:514, 1964.
5. Venables, A. W.: The syndrome of pulmonary stenosis complicating maternal rubella, Brit. Heart J. 27:49, 1965.
6. Rowe, R. D., Mehrizi, A., Elliot, H. L., and Neill, C. A.: Cardiovascular disease in the rubella syndrome. Cassels, D. E., editor: The heart and circulation in the newborn and infant, New York, 1966, Grune & Stratton, Inc., p. 180.
7. Hastreiter, A. R., Joorabchi, B., Pujatti, G., van der Horst, R. L., Patacsil, G., and Sever, J. L.: Cardiovascular lesion associated with congenital rubella, J. Pediat. 71:59, 1967.
8. Franch, R. H., and Gay, B. B., Jr.: Congenital stenosis of the pulmonary artery branches. A classification with post mortem findings in two cases, Am. J. Cardiol. 12:512, 1963.
9. Baum, D., Khoury, G. H., Ongley, P. A., Swan, H. J. C., and Kincaid, O. W.: Congenital stenosis of the pulmonary artery branches, Circulation 29:680, 1964.
10. Orell, S. R., Karnell, J., and Wahlgren, F.: Malformation and multiple stenoses of the pulmonary arteries with pulmonary hypertension, Acta Radiol. 51:119, 1960.
11. Rowe, R. D., and Lowe, J. B.: Auscultation in the diagnosis of persistent ductus arteriosus in infancy. A study of 50 patients, New Zealand Med. J. 63:195, 1964.
12. Agustsson, M. H., Arcilla, R. A., Gasul, B. M., Bicoff, J. P., Nassif, S. E., and Lendrum, B. L.: The diagnosis of bilateral stenosis of the primary pulmonary branches based on characteristic pulmonary trunk pressure curves, Circulation 26:421, 1962.
13. Patten, B. M.: The changes in circulation following birth, Am. Heart J. 6:192, 1930.
14. Danilowicz, D., Rudolph, A. M., and Hoffman, J. I. E.: Vascular resistance in the large pulmonary arteries in infancy (P), Circulation 32:74, 1965.

Experimental and laboratory reports

Isoproterenol induced acute experimental cardiac necrosis in the turtle (Testudo Horsfieldi)

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In most mammals, administration of isoproterenol induces acute cardiac necrosis.[1-3] Opinions on the mechanism of origin of this necrosis differ. According to Rona and associates the strong positive inotropic and chronotropic effect of isoproterenol followed by the blood pressure dropping leads to a pronounced disproportion between supply and consumption of oxygen in the heart muscle. According to Raab and colleagues substances with such an effect (catecholamines) cause relative hypoxia of heart muscle and necrosis. Rosenblum and co-workers[4] did not observe hemodynamic changes that might explain relative insufficiency of the coronary circulation after the administration of isoproterenol. According to their opinion, changes are mainly due to metabolic effects of this substance, perhaps on lipid metabolism. Finally, Handforth believes that necrosis after isoproterenol is due to ischemia. This hypothesis is supported by the finding[8] that necrosis develops in the same areas of cardiac tissue where local vasoconstriction occurs after application of necrogenic doses of isoproterenol. In previous work, we confirmed this finding and showed that local vasoconstriction disappears within one hour after isoproterenol administration. Others[1, 12] have shown that the occurrence of necrosis after isoproterenol can be limited by different inhibitors of monoaminooxidase. They explain the origin of necroses by interference of endogenous heart catecholamines with the effect of isoproterenol itself. Clementi and co-workers[12] assumed on the basis of electron microscopic observations that cardiac cells are injured by direct interaction between isoproterenol and contractile proteins. It follows, however, from the electron microscopic findings of Maruffo[7] that changes in muscle cells due to isoproterenol are very similar to those found in other hypoxic states.

These contradictions in the various hypotheses led us to examine the cardiotoxic effect of isoproterenol in Reptilian hearts. These have an anatomically distinct *outer* layer which is compact and supplied by coronary arteries. The inner *spongylike* part of this heart is supplied by diffusion from the intertrabecular spaces from the ventricular lumen.[14,15] If the

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mechanism of cardiotoxic effect of isoproterenol is mediated by intervention of this drug in coronary circulation, one can presume that the injured part of the Reptilian heart should be an outer compact layer supplied by coronary arteries.

Methods

A total of 62 sand turtles (Testudo Horsfieldi) was used. They were examined in July, November, and January. Active animals in the first [illegible] groups were kept at 23° C, the hibernating turtles, in January, at 11° C. The terminal vascular bed in the ventricular musculature was examined after injecting 30 per cent India ink with gelatine (40° C.) using an apparatus for applying constant pulsation pressure.[7] Injection was retrograde from the right aortic arch into the beating heart after rinsing with Ringer solution. After polymerization of the gelatine (cooling at 0° C.) the heart was removed and fixed in 10 per cent neutral formol.

Isoproterenol was given in 2 equal consecutive doses of 80 mg. per kilogram of body weight or 320 mg. per kilogram intraperitoneally during 48 hours into the region of the inguinal skinfold. Twenty-four hours after the second injection the animals were decapitated, the hearts were removed, weighed, and fixed in 10 per cent neutral formol. Macroscopic evaluations of cardiac necrosis[13] cannot be made in turtles. Hence material was examined histologically.

Histology. The India ink injected and fixed preparations were embedded into gelatine and cut with a freezing microtome into 25 μ slices and stained with hematoxylin. The noninjected hearts were cut in the frontal plane, embedded in paraffin, and slices of 5 μ were stained with hematoxylin-eosin, Masson's trichrom in combination with elastic staining, and the PAS reaction. Some preparations were also stained with Heidenhein's hematoxylin and reticular fibers were stained according to Gömöri.

Results

The turtle myocardium has 2 types of blood supply (Fig. 1). The internal spongy-like musculature is supplied by diffusion from the ventricular lumen via the intertrabecular spaces. The outer compact layer is supplied by the coronary artery which leaves the right aortic arch above the branching off of the aorta. Both layers are separated by a thin layer of connective tissue. No anastomoses between the coronaries and blood lacunae could be found.

Fig. 1. Blood supply of the turtle myocardium. A, Compact outer layer with vascular supply. B, Spongy inner layer with lacunar supply. India ink injection. (Hematoxylin; magnification ×100.)

Table I shows the necrogenic effect of isoproterenol on the turtle heart. In the July group (active animals) cardiac necroses were found in 2 out of 8 turtles given 2 × 80 mg. per kilogram of isoproterenol. In the November group (active animals) necroses were found in 4 out of 8 turtles receiving the same dose as the July group. A 4 times larger dose (320 mg. per kilogram per 48 hours) induced necrosis in 2 out of 8 animals. In the January group (hibernating animals) a dose of 2 × 80 mg. per kilogram per 48 hours induced necrosis in 3 out of 8 animals.

Table I. Acute cardiac necrosis (isoproterenol) in turtle males (Testudo Horsfieldi) (isoproterenol 2 × respective dose per kilogram of body weight per 48 hours)

Experimental group	*No.*	*IPRO dose (mg./Kg./48 hr.)*	*Body weight (Gr.) ± S.E.*	*Heart weight (mg.) ± S.E.*	*Heart ratio ± S.E.*	*Animals with necrosis*
						Total N of animals
July (active animals)	4	0	348 ± 19	714 ± 87	0.20 ± 0.02	0/4
July (active animals)	8	80	382 ± 40	773 ± 40	0.20 ± 0.003	2/8
November (active animals)	4	0	468 ± 93	1 181 ± 79	0.21 ± 0.01	0/4
November (active animals)	8	80	333 ± 15	703 ± 31	0.20 ± 0.002	4/8
November (active animals)	8	320	345 ± 9	664 ± 23	0.20 ± 0.01	2/8
January (hibernating animals)	8	0	205 ± 12	386 ± 26	0.19 ± 0.002	0/8
January (hibernating animals)	8	80	210 ± 12	386 ± 21	0.18 ± 0.001	3/8
Total number of animals treated by isoproterenol	32					11/32

There were no statistically significant differences in the incidence of necrosis between these 3 groups.

Microscopic findings. Changes induced by isoproterenol are mostly localized in the spongy-like musculature predominantly at the border of the compact outer layer (Fig. 2). Very rarely they are found in the outer compact part of the cardiac muscle. They appear as small disseminated coagulation necroses of muscle cells with a pronounced inflammatory infiltration (Fig. 3). This consists of eosinophil granulated heterophil leukocytes and mononuclear elements. Probably at least some of the mononuclear elements arise from the swollen endothelial lining of the trabeculae. Somewhere only this inflammatory infiltrate was found without visible necrosis of muscle cells. Free eosinophil granules from destroyed leukocytes are often present in otherwise intact muscle cells. The myocardium of control animals was normal; only occasionally was found nodelike thickening of the endothelial lining of muscle trabeculae.

Discussion

Isoproterenol-induced necrotic changes in the cardiac muscle have been described in homoiotherms. Isoproterenol has now been shown to cause similar changes in poikilotherms. Their localization, however, differed. In homoiotherm animals necroses are found subendocardially.[9,14] In the turtle they appear in the spongy-like inner musculature mainly at the border of the outer compact layer. The fact that necroses are localized preponderantly in the spongylike part of the cardiac muscle does not support the opinion of Handforth[9] that isoproterenol-induced cardiac necroses are due to a vascular mechanism and that they might be classified as ischemic necroses. In contrast to necroses in homoiotherm's heart were these in poikilotherms less extensive and never caused death. Nothing is known about the reaction of the coronary arteries of cold-blooded animals to isoproterenol. It is worth mentioning the paper of Juhasz-Nagy and colleagues[15] which indicate that there are differences in the reactivity of coronary vessels between poikilotherm and homoiotherm animals. In the turtle coronary vasoconstriction occurred after the administration of epinephrine but changes in cardiac activity (caused by increased temperature, hypoxia, etc.) did not induce increased coronary blood flow. This low

Fig. 2. Necrotic changes with mononuclear inflammatory reaction in the spongious part of the turtle heart. Similar changes in the outer compact layer of the heart are scarce. PAS reaction. (Magnification ×100.)

Fig. 3. Disseminated necroses of spongious myocardium. Mononuclear inflammatory reaction. PAS reaction. (Magnification ×135.)

adaptability of the coronary circulation in poikilotherms is explained by the different morphological structure of the terminal vascular bed in the turtle heart.[19] It is also possible that the amount of drug administered that reaches the heart tissue from the lacunae and coronary vessels differs, so that the resulting concentration of isoproterenol in the spongylike and compact layers is different. The volume ratio of spongylike tissue to lacunae may be different to the ratio of compact tissue to capillaries. Direct evidence is lacking. It is noteworthy that necrosis also developed in inactive animals. According to Privitera and Mersmann,[9] oxidative phosphorylation in isolated mitochondria from the turtle heart shows seasonal variations. The maximum is found in the Summer (July to August), the minimum in May, the difference being larger than 50 per cent. Changes in ambient temperature have similar effects. According to Clark and associates,[20] resting cardiac metabolism in poikilotherms is doubled when the temperature rises by 10° C.

Summary

1. Administration of isoproterenol to the turtle (Testudo Horsfieldi) in 2 equal doses during 48 hours causes acute necrotic and inflammatory changes in the myocardium.

2. Necroses are mainly localized in the internal spongylike musculature of the heart which is supplied by diffusion from the ventricular lumen. Necroses are found only exceptionally in the compact musculature supplied by coronary arteries. The changes are morphologically similar to those found in homoiotherms.

3 The incidence of necroses was independent on the seasonal activity of the animals.

4 The fact that necroses are localized in the part of the turtle heart where coronary supply is lacking supports the opinion that the necrogenic action of isoproterenol seems not to be caused solely by vascular mechanism.

REFERENCES

1. Chappel, C. I Rona, G Balazs, T and Gaudry R. Comparison of cardiotoxic actions of certain sympathomimetic amines, Canad J Biochem. Physiol. 37:35 1959
2. Rona, G., Chappel, C. I Balazs, T and Gaudry R. An infarct like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat, Arch. Path. 67:443 1959
3. Rona, G., Zsoter T Chappel, C., and Gaudry R. Myocardial lesions, circulatory and electrocardiographic changes produced by isoproterenol in the dog Rev canad. biol. 18:83 1959
4. Rona, G., Kahn, D S. and Chappel, C I Studies on infarct like myocardial necrosis produced by isoproterenol review Rev canad. biol. 22:241 1963
5. Raab, W Stark, E., MacMillan, W H and Gigee, W R. Sympathogenic origin and antiadrenergic prevention of stress-induced myocardial lesions, Am. J Cardiol 8 169 1961
6. Rosenblum, L, Wohl, A., and Stein, A. A Studies in cardiac necrosis. I Production of cardiac lesions with sympathomimetic amines, Toxic. Appl. Pharmacol. 7 1 1965
7. Rosenblum, I Wohl, A and Stein, A. A Studies in cardiac necrosis. II Cardiovascular effects of sympathomimetic amines producing cardiac lesions, Toxic. Appl. Pharmacol. 19 1965.
8. Rosenblum, L, Wohl, A and Stein, A A Studies in cardiac necrosis. III. Metabolic effects of sympathomimetic amines producing cardiac lesions, Toxic Appl. Pharmacol. 7:344 1965.
9. Handforth, C. P Isoproterenol-induced myocardial infarction in animals, Arch. Path. 73 161 1962.
10. Ošťádal, B and Poupa, O Occlusion of coronary vessels after administration of isoprenaline, adrenaline and noradrenaline, Physiol. Bohemoslov 16 116, 1967
11. Zbinden, G. Inhibition of experimental myocardial necrosis by the monoamine oxidase inhibitor isocarboxazid (Marplan) Am Heart J 60:450, 1960.
12. Leszkovszky G. P and Gál G. Observations on isoprenaline-induced myocardial necroses, J Pharm. Pharmacol. 19:226, 1967
13. Clementi, F Vafiry J and Peracchia, C. Ultrastructural observations of infarct-like lesions induced by isoproterenol, Titlbach M editor Electron microscopy (monograph) Prague, 1964 Academia, vol B pp. 103-104.
14. Maruffo, C. A. Fine structural study of myocardial changes induced by isoproterenol in Rhesus monkey (Macaca mulatta) Am. J Path. 60:27 1967
15. Juhasz Nagy A. Szentivanyi, M Szabo, M., and Vamosi, B Coronary circulation of the tortoise heart, Acta Physiol. Hung 23:33 1963
16. Brady A. J and Dubkin, Ch. Coronary circulation in the turtle ventricle Comp. Biochem. Physiol. 13 119 1964
17. Fedeler T A simple electric apparatus for automatic injection of vessels by pulsating pressure, Folia Morph. 13:423, 1965
18. Rona, G., Chappel, C. L, Balazs, T and Gaudry R The effect of breed, age and sex on myocardial necrosis produced by isoproterenol in the rat, J Geront. 14 169 1959
19. Privitera, C A and Mersmann, H. J Seasonal oxidative phosphorylation by turtle heart mitochondria, Comp. Biochem Physiol. 17 1045, 1966.
20. Clark, A. J Eggleton, M. G., Eggleton, P., Gaddie, R and Stewart, C P The metabolism of the frog heart, Oliver and Boyd, editors Edinburgh, 1938.

The ischemic zone surrounding acute myocardial infarction: Its morphology as detected by dehydrogenase staining

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Exact knowledge of the boundaries of the zones of sublethal injury and ischemia surrounding the region of myocardial infarction is of great interest to the electrocardiographer because of the theoretical relationship between such damaged myocardium and the classical alterations in the S-T segment and T waves following coronary occlusion. Similarly, the student of the ventricular pump would be benefited if the regions of subnormal contraction could be clearly labeled.

The decrease in cellular enzyme activity in areas of myocardial ischemic injury has been demonstrated previously by means of histochemical staining techniques.[1,2] In this study, an effort was made (1) to demonstrate the geographic distribution of altered dehydrogenase staining reaction in the myocardium distal to experimental occlusion of a coronary artery and (2) to examine the morphological progression of tissue damage in relation to the duration of circulatory embarrassment. The findings suggest that the geometry of a zone of intermediate damage can be delineated by dehydrogenase staining and can be so followed in time. The relationship between this zone and the zones of functional impairment (either electrical or mechanical) awaits further study.

Materials and methods

The anterior descending branch of the left coronary artery was doubly ligated and sectioned 3 cm. below its origin in a series of dogs, producing an area of myocardial ischemic injury predominantly confined to the antero-apical region of the heart. At timed intervals varying from 1 hour to 1 week after the initial operation histochemical staining techniques were applied to fresh frozen cold microtome sections of the myocardium to demonstrate cellular activity for 8 dehydrogenase enzymes.

Procedure. Thirty-three mongrel dogs which had been housed in air conditioned

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quarters and offered free access to food and water were submitted to thoracotomy under sterile conditions and under anesthesia with 30 mg. per kilogram of intravenous pentobarbital. Respiration through an endotracheal tube was maintained by means of an electric pump respirator. When an interval of 48 hours or more was expected between the initial surgery and death of the animal, 10 c.c. per pound of 5 per cent dextrose in water was administered intravenously during the operation. A portion of the anterior descending branch of the left coronary artery approximately 0.5 cm. long and approximately 3 cm. from its origin was dissected free from its accompanying vessel and occluded with double ligatures. The vessel was then cut through and the thoracic cavity closed. After a predesignated lapse of time, the animals were reanesthetized and the thoracic cavity reopened. The animals were then put to death by means of exsanguination while the heart was rapidly excised.

Immediate preparation of the heart for sectioning was accomplished by washing it in isotonic saline and cutting it into 1 cm. slices from apex to base. Each slice was then portioned into 1 to 2 cm. blocks for quick freezing with compressed CO_2. It was necessary to shave between 1 and 2 cm. of tissue from the surface of each block in order to obtain a section of tissue which would extend from the endocardial surface to the epicardial surface. (Careful attention was given to orientation so that the aspect of the ring nearest to the apex of the heart was "up" and sectioned first.) Sections 8 μ thick were cut from each tissue block on a Slee Clearview type "HS" cryostat and stained as described below to demonstrate intracellular dehydrogenase activity.

Since each tissue section was 8 μ in thickness and since no more than 15 sections were taken from each tissue block, the level of myocardium observed microscopically for ring 2, for example, ranged from a minimum of 10 mm. to a maximum of 15 mm. distal to the point of coronary ligation. This technique thus assured microscopic sections at sufficiently comparable levels in the ventricles of the different canine hearts.

In addition, sections were also stained with hematoxylin and eosin and pulmonary artery stenosis. Because droplets of neutral fat between the myofibrils in and around infarcted areas of myocardium take up the diformazan and could conceivably be mistaken for swollen mitochondria, control sections were stained with oil red O.

Staining techniques. In those sections which were stained with hematoxylin and eosin, nonspecific changes consisting of interstitial edema, the migration of a few neutrophils into congested vessels, and hyperemia of a few small venules and capillaries could be detected in areas of suspected myocardial ischemia as early as 1 to 2 hours after ligation of the vessel. As was suspected, however, no definite ischemic changes were discernible with hematoxylin and eosin until approximately 12 hours after the induction of the infarct when heavy margination of the infarcted area by neutrophils and shrinking acidophilia, and hyalinization of the myofibrils occurred. Irregular swelling of the A-bands and patchy loss of affinity for the stain could also be detected in some fibers at this time.

The mechanism of action of Nitro Blue Tetrazolium (BT) in dehydrogenase stains can be suggested by using as an example a simplification of the basic reaction which must take place for the demonstration of lactic dehydrogenase (LDH) activity. When lactic acid is oxidized to pyruvic acid in the presence of diphosphopyridine nucleotide (DPN), LDH and Nitro BT, the Nitro BT is reduced to a diformazan which is precipitated in the tissue at the site of enzyme activity.

Succinic dehydrogenase (SDH). The method for demonstrating SDH was modified after that by Nachlas and associates and Pearse. Incubation was maintained for 30 minutes in air at 37 degrees rather than at the previously recommended shorter interval.

DPN linked dehydrogenases. The demonstration of the DPN-linked dehydrogenases was accomplished by modifying the method of Hess, Scarpelli, and Pearse.[18] DPN was combined with the other constituents of the standard incubating medium as the last ingredient prior to adjustment of the pH with Tris buffer and incubation was held to 30 minutes at 37 degrees in air. With the exception of hydroxybutyric dehydrogenase, in which sodium

azide was used as the respiratory inhibitor all of the DPN linked dehydrogenases studied were demonstrated with sodium cyanide The following substrates were used in the incubating medium for the demonstration of the different dehydrogenase systems Hydroxybutyric dehydrogenase substrate DL-β hydroxybutyric acid sodium salt isocitric dehydrogenase substrate DL isocitric acid malic dehydrogenase substrate L malic acid glutamic dehydrogenase substrate sodium L-glutamate monohydrate glycerylphosphate dehydrogenase substrate sodium DL-β-glycerophosphate neutralized with 0 1 M HCl alcohol dehydrogenease substrate ethanol lactic dehydrogenase substrate sodium DL lactate Rinsing fixation and mounting were unchanged from the original recommendations.

In each case the evenly distributed black cobalt formazan deposits or deep purple diformazan deposits were judged to indicate activity of the respective enzyme system and to be intramitochondrial With the reservations noted below when the dots were fine (distinguishable under oil immersion) the mitochondria were estimated to be under 1 × 2 μ in size and normal when visible under high dry they were estimated to be at least twice normal in size and swollen (Fig 1)

In the discussion which follows the morphologic zones will be designated by the respective terms normal for the region of apparently unaltered enzyme activity and myocardial architecture "ischemic" for myocardium in which the only changes are swollen deeply stained mitochondria or A bands and necrotic for the central

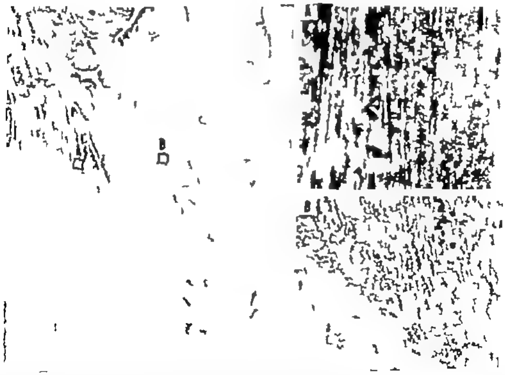


Fig 1 Three morphologic zones of myocardium The panel on the left shows a lower power view of the section of myocardium 24 hours after coronary artery ligation Tissue has been stained for lactic dehydrogenase activity The dark grey represents the normal zone the light grey the intermediate zone of ischemia, and the *pale unstained* tissue the central zone of necrosis. Inset *A* shows the boundary between the normal zone and the zone of ischemia. Note the undisturbed myocardial architecture in both zones. There is diffuse sarcoplasmic staining reaction in the normal region and mitochondrial swelling in the ischemic zone Inset *B* shows the boundary between the ischemic zone again characterized by the swollen black mitochondrial dots, and the central zone of necrosis characterized by absence of enzyme activity lack of mitochondria, and disruption of normal myocardial architecture. The original oil immersion magnification was ×800.

zone of architectural destruction and absence of dehydrogenase activity The term combined will indicate the total area of injured tissue including both the ischemic and necrotic zones.

Once the various morphologic zones had been defined the change in their respective sizes in relation to time could be evaluated. In order to estimate the relative proportion of each of the 3 zones, the involved area was reconstructed by taking photographs of each tissue section and then placing them in their appropriate positions in relation to the original cross-sectional myocardial ring as demonstrated in Fig 2. By joining the zonal boundaries in adjacent sections, we constructed fairly accurate diagrammatic representations of each involved myocardial ring A planimeter was then used to obtain numerical values for the area occupied by each of the 3 morphologic zones (Fig 3) From these values, estimates were obtained of the relative cross-sectional areas of each of the 3 zones with major attention directed to ring number 2.

With these histochemical stains, we were unable to demonstrate any variation in the pattern of loss between the 8 different dehydrogenase enzymes following circulatory embarrassment. The boundaries of the regions of altered staining in successive sections of a tissue block stained for different enzymes were consistently superimposable. For this reason separate quantitative description of the respective zones for each of the 8 enzyme stains does not appear and after 10 such complete sets of observations only 2 enzymes were employed in the remainder of the study The stains for LDH and HBD were chosen for this purpose because they offered greater contrast between the 3 morphological zones than did the other enzyme stains.

Nine of the 33 animals were excluded from the final study 3 because of inappropriate ligation due to anomalous distribution of the left anterior descending artery 4 because of unexpected death during the first 24 hours following thoracotomy and 2 because of faulty and uneven staining of the tissue sections traced to error in preparation of 1 of the reagents.

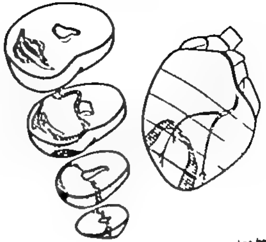
Results

The ischemic alteration in staining pattern for myocardial dehydrogenases By using

Fig 2 Reconstruction of myocardial ring using photographs of individual tissue sections.

Normal tissue □ Ischemic tissue ▣ Degenerating tissue □

Fig. 3. Diagrammatic representation of the 3 morphologic zones of myocardium seen microscopically in the myocardial ring represented in Fig. 2.



Normal tissue □ Ischemic tissue ▣ Degenerating tissue □

Fig. 4. Three-dimensional representation of the 3 typical morphologic zones of myocardium in myocardial infarction. The point of arterial ligation was just proximal to the superior border of the infarction on the surface of the heart.

histochemical staining for the demonstration of dehydrogenase activity, pathological changes in tissue were observed much earlier than with more conventional techniques as has been noted by others.

Following the induction of ischemia, the enzyme-stained myocardium could be separated into 3 relatively distinct morphologic zones (Fig. 1). There was a central area which showed disruption of the normal myocardial architecture and complete absence of all demonstrable enzyme activity. This area was surrounded by a second intermediate zone which showed large-dot mitochondrial swelling and A-band swelling but otherwise preservation of the normal myocardial architecture. The intermediate zone was in turn surrounded by normal cardiac tissue characterized by fine-dot mitochondria and A bands which had been maintained in their original state in the presence of normal myocardial architecture. The distinction between large-dot and fine-dot was an easy one in practical terms: the large dots were readily visible under high dry (×320) but the fine dots required oil immersion for resolution (×800). The uninjured tissue also exhibited a rather diffuse sarcoplasmic staining reaction which was not seen in the 2 zones of ischemic injury. The configuration of relatively pure regions could be suspected from gross examination of microscopic slides: necrotic areas were clear and colorless, normal myocardium appeared violet-blue (resulting from the combination of mitochondrial blue-black and the pinker sarcoplasmic stain), but myocardium of intermediate injury appeared a deep cobalt blue (from the intense mitochondrial stain without the sarcoplasmic component). Microscopic inspection was necessary, however, in the borderlands and for the detection of small enclaves of normal fibers in predominantly ischemic regions or vice versa.

Though not present in abundance in normal dog myocardium, neutral fat droplets (1 to 2 μ) were commonly seen on the periphery of the ischemic zone. When the respective stains were applied to successive sections of myocardial tissue, the distribution of the neutral fat droplets in oil red O stains could be seen to be sparse and irregular compared with the distribution of the swollen mitochondria demonstrated by the enzyme stains. The swollen mitochondria present in ischemic zones as seen with the enzyme stains were also more uniform in size than were the more lightly stained fat droplets.

When the microscopic findings were projected into a three-dimensional representation of the heart, it was observed that ligation of the canine anterior descending

Table I Cross sectional areas in myocardial ring slice 1 to 2 cm above apex of left ventricle

Time	Dog No	Sex	Body wt. (Kg)	Area of ring (cm²)	Area of ischemia (cm²)	Area of necrosis (cm²)	Area of combined injury (cm²)	Ischemic / Combined %	Combined / Whole %
Control	17	M	17.7	10.39	0	0	0	—	—
	22	F	15.0	6.44	0	0	0	—	—
1 hour	18	M	18.1	17.22	0	[illegible]	0	—	—
	20	F	15.4	15.19	0	0	0	—	—
	28	M	17.7	14.34	0	0	0	—	—
3 hours	25	M	15.9	7.43	0	0	0	—	—
6 hours	16	M	18.6	15.71	3.06	0	3.06	100	19.5
	27	M	15.4	6.[illegible]	1.14	0	1.14	100	16.6
12 hours	12	M	23.6	23.73	3.27	3.85	7.12	45.9	31.3
	23	M	20.4	14.02	1.35	0.62	1.97	68.5	14.0
[illegible] hours	10	M	18.1	10.49	2.90	2.19	5.09	57.0	48.5
	11	M	22.2	17.66	4.28	4.72	9.00	47.6	51.0
	32	M	10.9	8.18	1.20	0.97	2.17	55.3	26.6
24 hours	8	M	19.5	20.43	1.47	2.17	3.64	40.4	17.8
	13	F	17.7	14.45	2.21	1.82	4.03	54.9	27.9
	21	M	17.2	14.10	1.37	1.97	3.34	41.0	23.7
	24	M	14.3	8.24	0.85	1.22	2.07	41.0	25.1
	31	M	14.1	9.85	1.01	1.72	2.73	37.1	27.7
48 hours	6	F	23.6	13.43	1.49	2.79	4.28	34.8	31.9
	14	M	12.7	10.[illegible]	1.06	1.87	2.93	36.2	28.8
7 day	19	M	11.8	9.15	0.89	1.70	2.59	34.4	28.3
40 day	30	M	12.7	13.72	0.0	1.37	1.37	0.0	10.0

artery results in infarction around the right ventricle as well as the antero-apical portion of the heart. Furthermore, the infarct in the deeper portions of the myocardium extended toward the cardiac base above the point of ligation (Fig. 4).

Temporal evolution of the staining reaction following coronary ligation. Planimetric measurements of the cross-sectional areas of the 3 morphologic zones were made from reconstructions of the ring slices. The areas of the zones for ring 2 (approximately 0.5 to 1.0 cm below the site of coronary ligation) are listed for 22 animals in Table I. The results are grouped according to the duration of the ischemia. No reproducible pathological changes in the myocardial tissue were detected with the histochemical stains until 6 hours after coronary artery ligation. At that time the zone of injured tissue showed only ischemic changes, consisting of the swollen mitochondria and A-bands, loss of extra mitochondrial enzyme activity and preservation of the normal myocardial architecture. Twelve hours after ligation degeneration of the mitochondria and A-bands began to take place. This degeneration was observed to be within the area of initial change and was completely separated from the undamaged myocardium. The combined area of injured tissue occupied a larger portion of the heart at 12 hours than it had at 6 hours. At 18 hours after vascular interruption that portion of the myocardium which had undergone complete degeneration occupied a relatively larger section of the heart as did that portion showing only ischemic change, but the relative increase was much greater for the former. The combined area of injury reached its maximum size at 18 hours and subsequently began to regress. The area of necrosis continued to enlarge however at the expense of the ischemic tissue which was eventually reduced at 1 week after infarction to a narrow ring separating intact myocardium from the necrotic tissue. The morphological progression of these various stages of tissue damage is illustrated in Figs. [illegible] and 6.

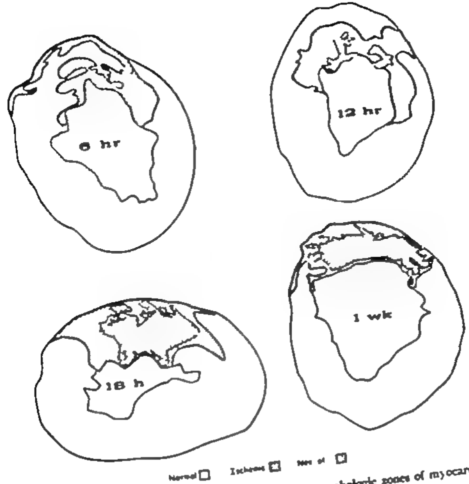


Fig. 5. Diagrammatic representation of the relative sizes of 3 morphologic zones of myocardium at varying intervals fter coronary artery ligation.

Discussion

Mitochondrial swelling in myocardial cells has been demonstrated by use of the electron microscope within a half hour fol lowing coronary ligation.[11,12] Several hy potheses have been proposed to explain this swelling in response to ischemic injury. Many investigators have attributed the swelling to an increased permeability of the mitochondrial membrane, probably as a result of accelerated electron transport within the mitochondria and rapid depletion of energy rich phosphate bonds.[14,15]

In our description of the microscopic characteristics of the various morphological zones, it was noted that in normal myocardial tissue a rather diffuse sarcoplasmic staining reaction was present but with the onset of tissue hypoxia this sarcoplasmic staining reaction disappeared to be replaced by heavily stained swollen mitochondria. Since the mitochondrion is considered to represent the site of the enzymes responsible for the tricarboxylic acid cycle[16] more enzyme activity would be expected in the normal myocardial tissue than in the ischemic zone. The difference in intensity of staining suggests a paradox in which the mitochondria of normal tissue appear to show less enzymatic activity than do the mitochondria of ischemic tissue. We feel that no such paradox should be inferred the deeper staining is probably the result of an increase in the permeability as well as surface area of the mitochondrial membrane following ischemic injury. This increased permeability allows more of the dye to enter the mitochondrion with the result that the

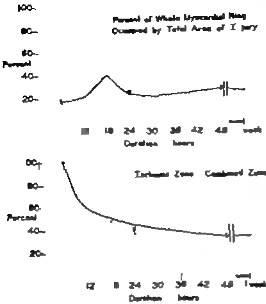


Fig. 6. In the upper graph is plotted the per cent of the whole myocardial ring occupied by the combined or total area of injury (upper line). Note, that at 18 hours after coronary ligation, there is the suggestion of a peak in the size of the combined area of injury with subsequent regression.

In the lower graph is plotted the ratio of the ischemic zone to the combined area of injury. Note, that at 6 hours after ligation, the combined area of injury is occupied by ischemic tissue only, followed by the subsequent decrease in the area of the ischemic zone.

Both graphs suggest that the necrotic zone continues to enlarge, however, at the expense of the ischemic zone so that at 1 week, the ischemic zone occupies a relatively small portion of the injured tissue.

enlarged more heavily stained injured mitochondrion becomes easily visible under the light microscope.

Histochemical changes which occur in the myocardium after interruption of the blood supply have been described by several investigators,[4, 11, 12] but little attempt has been made to separate the heart into different microscopic regions based upon the morphology and integrity of the sites of intracellular dehydrogenase activity. Lushnikov[4] briefly mentioned the evolution of 3 zones of myocardial tissue following induced ischemia with respect to the level of enzyme activity. He described the development of an intermediate zone in which a reduction of the dehydrogenase activity and a decrease in the number of formazan granules had taken place separating normal tissue and the center of the developing infarct. He did not, however, describe the microscopic changes in morphology which had taken place in this intermediate zone and which constitute a more valid basis for differentiation since histochemical staining techniques do not yield reliable results regarding the levels of enzyme activity or the number of mitochondria present as only 1/3 to 1/2 of them can be identified in this manner.[9]

It would be desirable to study variations in the rate of depletion of the various cellular dehydrogenase enzymes and subsequently to correlate this data with the pattern of loss of those enzymes. Although the stains for various enzyme systems always showed identical patterns of altered activity, some enzyme systems stained more intensely than did others. However, the relative intensities within each system were highly comparable. By this technique, we are thus unable to state whether variable enzyme leaks occurred during the ischemic period of mitochondrial swelling prior to the time of absolute loss of detectable enzyme activity. It is well known clinically that the curves of rise and fall in serum level vary for different enzymes following myocardial infarction. Recent reports, however, suggest that the serum curve may be highly dependent upon removal of the enzymes from the serum by the reticuloendothelial system.[22, 23]

We feel that (1) the evidence presented by others indicating that when the mitochondrion is made ischemic it undergoes a critical change in size rendering it identifiable by high-dry light microscopy,[11-13] (2) the identification of dehydrogenase activity in the mitochondrion by diformazan deposits electron-microscopically, and (3) the demonstration of a qualitatively and distributively different pattern of dye deposit for neutral fat droplets together constitute an adequate basis for tentatively characterizing the "large-dot" zone as the zone of mitochondrial swelling and early myocardial ischemia. We have not independently confirmed their ultramicroscopic identification or subcellular localization but believe based on the work of others that the most likely explanation for the consistent

appearance of the large dots in the ischemic zone is that they are swollen mitochondria. Mitochondrial swelling is nonspecific and occurs in response to other insults but in the proper context may provide the major basis for the geographic identification of an intermediate degree of response to local myocardial ischemia. This technique offers a method for exact anatomic localization of certain effects of ischemic injury less severe than muscle necrosis. It may provide a useful tool in the study of possible reversing agents in myocardial infarction and in the correlation of cellular damage with electrophysiological alterations.

Summary

The distal 1/3 of the anterior descending branch of the left coronary artery in 33 pentobarbital-anesthetized dogs was ligated and subsequently fresh frozen cold microtome sections of ventricular myocardium were studied for enzymatic activity. The state of dehydrogenase activity correlated morphologically with severity of local ischemia: destruction of architecture was accompanied by loss of enzymatic activity while unaltered myocardium was characterized by a "fine-dot" pattern of enzyme staining. These dots were interpreted as moderately stained mitochondria measuring up to 1 μ in diameter and 2 μ in length. In a third intermediate zone completely separating the first 2 a "large-dot" pattern appeared which was interpreted as resulting from mitochondria which were swollen to twice the normal size and more intensely stained. Stains for all 8 dehydrogenase enzymes studied responded similarly to the circulatory embarrassment. A band swelling and accumulation of neutral fat droplets were observed in this third zone but the architecture was otherwise undisturbed.

The comparative size of the respective zones varied with the duration of the ischemic insult. Six hours after ligation only the normal and intermediate zones were found, but as architectural deterioration developed the size of this ischemic region gradually shrank to less than half of the abnormal myocardium. The injured region reached its maximum at 18 hours and subsequently regressed until 24 hours, after which it remained relatively constant.

The zone of myocardial ischemia as identified by altered dehydrogenase staining, remains to be characterized as to its functional capacity with regard to either electrical or mechanical activity.

We are indebted to Dr. Lorin Alger for his making available laboratory space in which to perform the histochemistry in this study. We also thank Dr. Blase Favara for the electrophoretic identification of lactic dehydrogenase isoenzymes in selected samples.

REFERENCES

1. Kent, S. P., and Diseker, M.: Early myocardial ischemia. Study of histochemical changes in dogs, Lab. Invest. 4:398, 1955.
2. Wachstein, M., and Meisel, E.: Succinic dehydrogenase activity in myocardial necrosis, Am. J. Path. 31:353, 1955.
3. Jennings, R. B., Kaltenbach, J. P., and Smetters, G. W.: Enzymatic changes in acute myocardial ischemic injury, Arch. Path. 64:10, 1957.
4. Kaufman, N., Gavan, T. L., and Hill, R. W.: Experimental myocardial infarction in the rat, Arch. Path. 67:482, 1959.
5. Hecht, A., Korb, G., and David, H.: Vergleichende histochemische, fluorescenzmikroskopische und elektronenoptische Untersuchungen zur Frühdiagnose des Herzinfarktes der Ratte, Virchow Arch. Path. Anat. 334:267, 1961.
6. Lamb Ikov, F. F.: Histochemical study of experimentally produced myocardial infarction, Fed. Proc. (Translation Supplement) 22:T906, 1963. Arkh. Pat. Vol. 4, No. 1, p. 55, 1962.
7. Shnitka, T. K., and Nachlas, M. M.: Histochemical alterations in ischemic heart muscle and early myocardial infarction, Am. J. Path. 42:507, 1963.
8. Nachlas, M. M., Tsou, K. C., de Souza, E., Cheng, C. S., and Seligman, A. M.: Cytochemical demonstration of succinic dehydrogenase by the use of a new p-nitrophenyl substituted ditetrazole, J. Histochem. Cytochem. 5:420, 1957.
9. Pearse, A. G. E.: Histochemistry: Theoretical and applied, Boston, 1961, Little Brown & Company.
10. Hess, R., Scarpelli, D. G., and Pearse, A. G. E.: Cytochemical localization of pyridine nucleotide-linked dehydrogenases, Nature (London) 181:1531, 1958.
11. Bryant, R. E., Thomas, W. A., and O'Neal, R. M.: An electron microscope study of myocardial ischemia in the rat, Circulation Res. 6:699, 1958.
12. Caulfield, J., and Klionsky, B.: Myocardial ischemia and early infarction: An electron microscope study, Am. J. Path. 35:489, 1959.
13. Suzuki, T., Yasuda, H., Yamaguchi, H., Muramatsu, H., and Takaki, F.: Electron microscope cyto-histopathology. (V) Electron microscope studies on experimental myocardial infarction in dogs, Jikeikai Med. J. 8:14, 1961.
14. Hunter, F. E., Jr., Levy, J. F., Fink, J., Schutz, B., Guerra, F., and Hurwitz, A.: Studies on

the mechanism by which anaerobiosis prevents swelling of mitochondria in vitro: effects of electron transport chain inhibitors, J. Biol. Chem. 234:2176, 1959.

15. Lehninger, A. L.: Reversal of thyroxine-induced swelling of rat liver mitochondria by adenosine triphosphate, J. Biol. Chem. 234:2187, 1959.
16. Chappell, J. B., and Greenville, G. D.: Mitochondrial swelling and electron transport, Biochem. Biophys. Acta 38:483, 1960.
17. Lehninger, A. L.: Ionic environment and the contraction of isolated rat-liver mitochondria by adenosine triphosphate. Biochem. Biophys. Acta 48:324, 1961.
18. Packer, L.: Metabolic and structural states of mitochondria. Regulation of phosphate, J. Biol. Chem. 236:214, 1961.
19. Miller, A. T., Conoly, D. M., Gabriel, M., and Handy, M. S.: Mitochondrial regulation of tissue respiration, Am. J. Physiol. 197:633, 1959.
20. Guyton, A. C.: Medical physiology, ed. 2, Philadelphia, 1961, W. B. Saunders Company.
21. Porter, K. R., and Franzini-Armstrong, C.: The sarcoplasmic reticulum, Sci. Amer. 212:73, 1965.
22. Fleischer, G. A., and Wakim, K. G.: The fate of enzymes in body fluids—an experimental study. IV. Relationship of the reticuloendothelial system to activities and disappearance rates of various enzymes, J. Lab. & Clin. Med. 61:107, 1963.
23. Notkins, A. L., and Scheele, C.: Impaired clearance of enzymes in mice infected with lactic dehydrogenase agent, J. Nat. Cancer Inst. 33:741, 1964.

Effects of norepinephrine and phenylephrine on myocardial energetics

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The mechanism whereby catecholamines increase myocardial oxygen consumption is not clear. It has been suggested recently[1] that the calorigenic or "oxygen wasting" effects of catecholamines on the heart[2] are explicable on a mechanistic basis, a result of altered hemodynamic parameters. However, it is not clear whether the inotropic effect of catecholamines leads to an altered oxygen requirement as a result of changes in mechanical work, ventricular force, rate of myocardial contraction, or efficiency of energy utilization. Since most previous studies have been conducted in isolated muscle strips or *in situ* preparations, the studies here reported were undertaken in an attempt to clarify the significance of these changes in the intact dog. A pure β-adrenergic drug such as isoproterenol has been studied partially[3,4] and differs from the action of norepinephrine in that it has greater chronotropic effect while not increasing ventricular systolic force or pressure.[5] Norepinephrine was chosen in these studies because it represents the natural neuroendocrine transmitter with physiological inotropic effect in stimulating increases in both force and velocity of contraction.[7] This was compared with phenylephrine, a synthetic sympathomimetic amine having primarily α-adrenergic activity, one which might be expected to increase ventricular pressure and force by inducing peripheral vascular constriction without directly influencing the inotropic mechanism of cardiac contraction. Thus, any difference in effects between the norepinephrine and phenylephrine could be ascribed to the inotropic effects rather than afterload or other biochemical action. Conversely, a failure to find significant differences in the relation between hemodynamic effects and energy cost would imply that the effects of both types of catecholamines could be ascribed entirely to the change in the hemodynamic parameter.

Materials and methods

A total of 20 fasted mongrel dogs were anesthetized with morphine sulfate intramuscularly (3 mg. per kilogram) followed in 20 minutes by intravenous pentobarbital (15 mg. per kilogram). Catheters were

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passed under fluoroscopic control into the left ventricle, ascending aorta, coronary sinus, and inferior vena cava. A Sones catheter (No. 4F or 6F) was placed in the left coronary artery. The distribution of injected test contrast media through this catheter was generally to both the left anterior descending coronary artery and the left circumflex artery, but occasionally one branch or the other received all the contrast material visible. The position of this catheter and the coronary sinus catheter was checked fluoroscopically and at autopsy at the conclusion of each experiment. Two experiments in which the coronary sinus catheter was within 1 to 2 cm. of the coronary ostium were discarded. Pressures were monitored with Statham P23Db strain gauges on an Electronics for Medicine DR-8 recorder.* The zero point was at the estimated level of the right atrium. In nine studies, the left ventricular pressure was monitored by using a Statham SF 1 or Dallons-Telco intracardiac manometer balanced and calibrated frequently against the same pressure recorded simultaneously with an external Statham P23Db manometer. In these instances, an electronic R-C differentiating circuit* was used to determine the first derivative of the left ventricular pressure, and percentage change from control was recorded. Pressure and heart rate measurements were averaged from at least five beats in each experimental period. A No. 4 polyvinyl thermistor catheter† with a time constant in flowing liquid of 0.13 second was placed in the ascending aorta. Ventricular volume was estimated by injecting small volumes (2 to 8 ml.) of cold saline into the left ventricle and recording the thermodilution curve in the ascending aorta. An average of 17 ± 8 step-functions were recorded in each experimental period and the ratio of each pair of steps determined. The mean and standard deviation of each set of ratios per experimental period was calculated; the latter averaged 0.05 ± 0.04. From these data, the error of the ratio ESV/EDV was calculated to be less than 5 per cent in 31 of the 43 determinations and less than 10 per cent in all cases except two. The end-diastolic volume so measured is considered to represent not so much an accurate determination of volume as an index of relative change.[11] Cardiac output was measured by a dye dilution technique in duplicate, using a Gilford cuvette densitometer. The deviation from the mean value of each pair of determinations averaged 5.8 ± 4.8 per cent.

Coronary blood flow was measured in 20 experiments by the technique of Herd and associates.[12] After rapid injection of 1 to 2 ml. of krypton-85 (Kr^{85}) (gas-in-saline*) directly into the left coronary artery catheter, the decay of radioactivity over the precordium was monitored with a two-inch scintillation detector probe, recording through a Picker transistorized ratemeter using a two-second time constant and strip chart recorder. The curve, replotted on semilog paper, showed a linear decay slope in all instances beginning from 15 to 60 seconds after injection and persisting for at least 1 to 1½ minutes. The half time was determined graphically and divided into 0.693 to give K, the coronary flow per 100 gram left ventricle per minute (corrected for the specific gravity, 1.05 of heart muscle). A partition coefficient of 1.0 was assumed. This determination was performed in duplicate for each experimental period with a mean deviation between pairs of 8.3 ± 8.0 ml. or 7 per cent. In 22 of these determinations, it was possible to calculate the coronary flow by planimetric integration of the entire Kr^{85} decay curve according to the suggestion of Zierler.[13] The values for coronary flow were generally lower by an average of 11 per cent at all levels of flow but were linearly correlated ($r = 0.88$, $p < 0.001$) with those calculated from the initial exponential decay. Since in some early experiments, the peak of the Kr^{85} curve was allowed to run off scale briefly, not all curves were amenable to planimetric calculations; however, a good exponential decay was observed as soon as the curve came onto the scale of the strip chart and the value obtained by semilog plot was therefore used in all studies. The agreement observed by Gorlin and Taylor[14] in a few cases between clearance of Kr^{85} after intramyocardial injection and clearance after

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intracoronary arterial injection suggests that the Kr[85] washout technique is measuring tissue flow rather than physiological "shunt" flow. In preliminary experiments arteriovenous differences of I[131] antipyrine were used as a measure of coronary flow. The results were similar qualitatively to the experiments in which Kr[85] was used, although were not considered as accurate or reproducible, particularly at higher flow rates, and so are not presented here.

Samples of arterial and coronary venous blood were obtained during the inscription of the coronary flow curve and analyzed for oxygen content manometrically in duplicate. Samples of blood for lactate and pyruvate were taken rapidly with appropriate precautions, immediately placed in iced 10 per cent perchloric acid, and the filtrate frozen until analyzed in duplicate by enzymatic technique. At the conclusion of each experiment the heart was removed and the left ventricle, including interventricular septum, was trimmed free of gross fat and valve tissue and weighed.

When all catheters were properly positioned, measurements were made of left ventricular pressure, output, volume, coronary flow, and myocardial $\dot{V}_{O_2}$ during an initial control period. Then norepinephrine* 0.5 to 2.9 μg per kilogram per minute or phenylephrine† 2.8 to 56 μg per kilogram per minute was infused intravenously until a steady change in ventricular pressure, heart rate, or dp/dt was observed. No attempt was made to adhere to a fixed dose, a fixed physiological response, or to develop a dose-response relationship. In four cases atropine was given intravenously as a single injection (0.1 to 0.2 mg.) in addition to phenylephrine infusion to negate the reflex bradycardia. When a steady state of ventricular response was achieved, usually within 10 to 15 minutes, the same measurements were repeated. Although it would have been desirable to compare effects of both norepinephrine and phenylephrine serially in the same animal, preliminary studies showed, as have others, that a prolonged hypotensive period and low cardiac output ensued when either drug was discontinued. Only one animal was therefore studied in this way. Studies were generally completed within one hour after beginning the catecholamine infusion to avoid the deleterious effects of prolonged infusion.[17]

Calculations

1. Volume.[11] (a) End-diastolic volume (EDV) (ml.) =

$$\frac{SV}{1 - (Tn/Tn - 1)}$$

where SV = stroke volume calculated from cardiac output divided by heart rate. Tn/Tn − 1 is the ratio of the directly recorded thermodilution step-functions.

(b) End-systolic volume (ESV) (ml.) = EDV − SV.

(c) Mean systolic volume ($\bar{V}$) (ml.) = ½ (EDV + ESV).

2. Force.[21] (a) Mean systolic force (MSF) (dynes × 10⁴) =

$$\pi r^2 \times LV_{sm} \times 1{,}332$$

where r (cm.) is the mean inner systolic radius calculated from the mean systolic ($\bar{V}$) assuming the left ventricle to be a sphere. LV_{sm} is left ventricular systolic mean pressure in mm. Hg. 1,332 is the mercury and gravity conversion factor.

(b) Force-time per beat (FTB) (dyne-sec. × 10³) = MSF × sep, where sep = systolic ejection period in seconds, measured from the aortic pressure pulse.

(c) Pressure-time per beat (PTB) (mm. Hg sec.) = LV_{sm} × sep.

3. Work. (a) Stroke work (SW) (Gm.-cm./bt.) = SV × (LV_{sm} − LV_{edp}) × 1.36 where LV_{edp} is left ventricular end-diastolic pressure in mm. Hg.

(b) Contractile-element work (CEW) index[22] (dyne-cm. × 10⁴) = LV_{sm} (SV + $\bar{V}$/9.6).

4. Power. (a) Stroke power (SP) (Gm.-cm./sec.) = SW/sep.

(b) Contractile-element power (CEP) (dyne-cm. × 10⁴/sec.) = CEW/sep.

5. Fiber shortening. (a) Distance (FSD) (cm.) = 2π (r_{ed} − r_{es}), where r_{ed} and r_{es} are inner radii at end-diastole and end-systole respectively of the assumed ventricular sphere.

Some authors have used different estimates of mean volume assuming ... change of volume ... data,[20] derived from measured change of transverse circumference, suggest ... decrease of volume, and therefore the arithmetic mean was used.

*Levophed bitartrate, Winthrop Laboratories, N. Y.

†Neo-Synephrine hydrochloride, Winthrop Laboratories, N. Y.

(b) Fiber shortening rate (FSR) (cm./sec.) = FSD/sep. FSD and FSR represent mean shortening along the inner circumference of the assumed spherical ventricle.

6 Energy cost (a) Aerobic—left ventricular oxygen consumption ($\dot{V}_{O_2}$) (ml./beat) = $(A-CV)_{O_2} \times CF \times LV$ weight $\times$ 100 where $(A-CV)_{O_2}$ is the coronary arteriovenous oxygen difference in volumes per 100 ml. and CF is the coronary flow ml./100 Gm./beat. Basal myocardial oxygen consumption is not subtracted

(b) Anaerobic—excess lactate (XL)[10] = $(L_{cv} - L_a) - (P_{cv} - P_a)$ (La/Pa) where La and Pa are the arterial lactate and pyruvate concentrations (mm./L.) and L_{cv} and P_{cv} are the corresponding simultaneous values in coronary venous blood

(c) Mechanical external efficiency (ME) (per cent) =

$$\frac{SW}{\dot{V}_{O_2} \times 2.06}$$

where 2.06 is the conversion factor for work performed per ml. O_2

Results

Control In the control state, $\dot{V}_{O_2}$ averaged 0.080 ± 0.03 ml. per beat. This value correlated significantly with several measured parameters including stroke work (r = 0.81) and stroke power (r = 0.79) (Fig 1) and contractile element work (r = 0.77) and power (r = 0.79) (Fig 2) Lesser but significant correlations with $\dot{V}_{O_2}$ were also obtained with force-time per beat (r = 0.68) (Fig 3) pressure time per beat (r = 0.52) and stroke volume (r = 0.74) although the differences from the parameters of work and power were not statistically significant. The correlations of $\dot{V}_{O_2}$ with fiber shortening rate and distance were not significant.

Catecholamine infusion Mean $\dot{V}_{O_2}$ increased during norepinephrine infusion to 0.119 ± 0.05 ml. per beat and decreased to 0.067 ± 0.03 ml. per beat during phenylephrine infusion. A significant ($p < 0.02$) correlation of $\dot{V}_{O_2}$ with work and power parameters (Figs. 1 and 2) continued to be observed for both norepinephrine and phenylephrine as in the control state except for the $\dot{V}_{O_2}$ versus CEW during phenylephrine action. In contrast was the absence of correlation with pressure or force parameters (Fig 3) or percentage change in rate of rise of pressure.

The ordinate intercept of the regression equation for $\dot{V}_{O_2}$ versus stroke work (Fig 1 *A*) was + 0.037 ml. per beat during the control state and + 0.034 during phenylephrine infusion. During norepinephrine infusion however the intercept value increased to + 0.065 ml. per beat. Almost identical intercept values were obtained from the regression equation for $\dot{V}_{O_2}$ versus contractile element work (Fig 2 *A*) The intercept value for $\dot{V}_{O_2}$ versus stroke power (Fig 1 *B*) was similar to the intercept for $\dot{V}_{O_2}$ versus contractile element power (Fig 2, *B*) during both the control state and norepinephrine infusion. Moreover the norepinephrine intercept was now the same as that for the control and phenylephrine regressions.

The slopes of the regression of $\dot{V}_{O_2}$ versus stroke work or stroke power (Fig 1 *A* and *B*) were similar during norepinephrine and phenylephrine infusions, although they were somewhat flatter than the corresponding control slopes.

Directional changes of $\dot{V}_{O_2}$ in individual experiments were compared with changes in the parameters mentioned above. As with the data from different animals lumped into control and experimental states the change in $\dot{V}_{O_2}$ was frequently not correlated with mean systolic force, pressure-time per beat, or force time per beat (Fig 4) In many cases, there was a marked increase in pressure time or force time with phenylephrine but nevertheless a decrease in $\dot{V}_{O_2}$. Conversely a number of experiments with norepinephrine show increases in $\dot{V}_{O_2}$ with only minimal increase or even decrease of pressure-time or force-time. Change in $\dot{V}_{O_2}$ when compared with change in FSR or work and power functions (Figs. 5 and 6) showed more concordance, that is, points fell in the right upper quadrant or left lower quadrant. A highly significant correlation ($p < 0.001$) was achieved for these functions (FSR = 0.62 SW = 0.64 SP = 0.61 CEW = 0.58 and CEP = 0.53) whereas there was *no* correlation for the force parameters. Plotting these data as percentage change from control yielded essentially

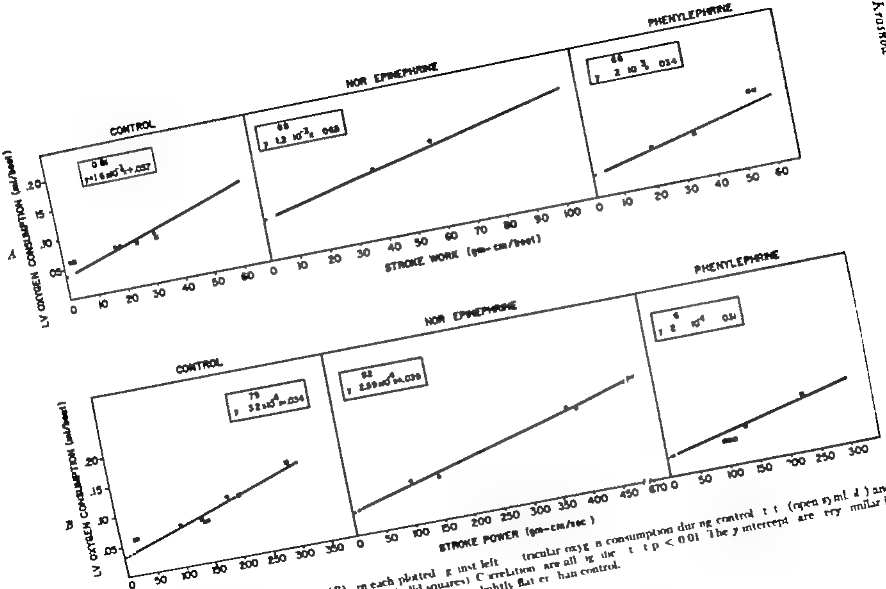


Fig 1 Stroke work (A) and troke pow (B) ro each plotted g inst left tricular oxyg n consumption dur ng control t t (open sy ml l) and norepinephrine (solid circles) or phenylephrine inf ion (solid squares) C rrelation are all ig the t t p < 0 01 The y intercept are ery milar in all tates in the power correlation. The slopes of experimental dat are slightly flat er han control.

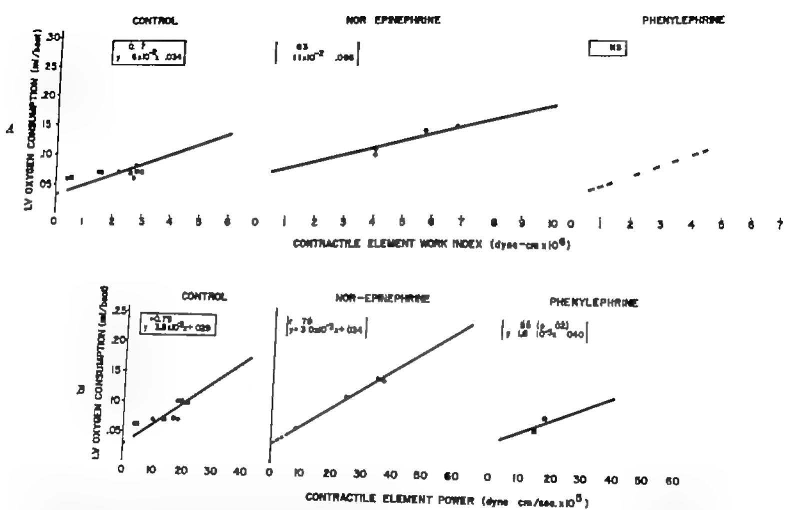


Fig. 2. Contractile element work index (A) and contractile element power index (B) are plotted as in Fig. 1. The few phenylephrine points do not achieve an independent regression of statistical significance but are plotted in relation to the control regression line. As in Fig. 1, the ordinate intercepts of the CEW index for norepinephrine deviate from control but not with the CEP index.

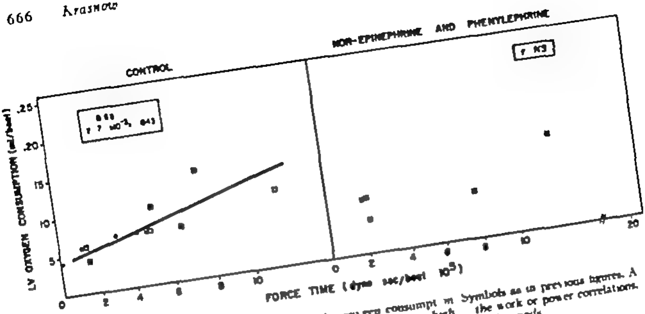


Fig. 3. Force-time is plotted against left ventricular oxygen consumption. Symbols as in previous figures. A significant correlation is observed in the control state, though not as high as the work or power correlations. However there is no significant correlation during the catecholamine experimental periods.

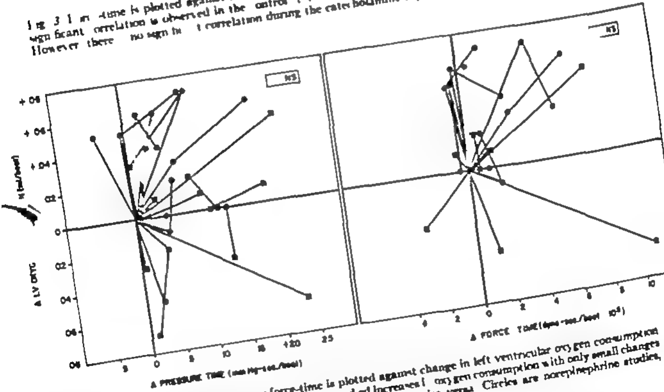
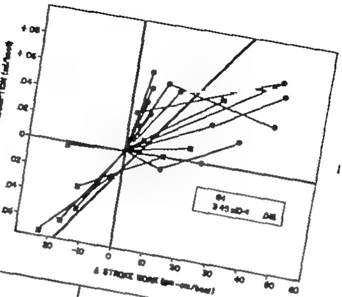


Fig. 4. Change in pressure-time or force-time is plotted against change in left ventricular oxygen consumption of individual experimental sequences. Note the marked increases in oxygen consumption with only small changes (sometimes *decreases*) in the pressure-time or force-time and vice versa. Circles are norepinephrine studies, squares phenylephrine.

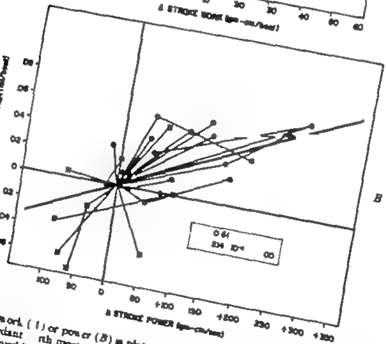
similar results. Increase in dp/dt was only directionally related to percentage increase in V_{O_2} (Fig. 7).

Stroke work correlated closely ($r = 0.96$) with contractile element work (Fig. 8). The same is of course true for stroke power and contractile element power since both are derived from the same systolic ejection period.

Myocardial anaerobiosis stimulated by catecholamines was observed in only four experiments. Increased ratios of lactate to pyruvate in coronary venous blood compared to arterial blood were reflected in



A



B

Fig. 5. Changes in stroke work (A) or power (B) is plotted against change in left ventricular oxygen consumption. The data are concordant with most points falling in upper right or lower left quadrants. A highly significant correlation is achieved for these incremental values compared to Fig. 4. Symbols as in Fig. 4.

small positive calculated excess lactate values of 0.29, 0.85, 0.51, and 1.00 millimoles per liter. Three of these instances occurred during norepinephrine infusion and one during phenylephrine stimulation. The coronary arteriovenous differences for lactate was reversed, i.e. lactate was produced in only one of these instances.

Discussion

The mechanism and determinants of energy requirement in muscular contraction skeletal or cardiac are imperfectly understood. In amphibian skeletal muscle the work of A. V. Hill[31] and others[32-34] over the last four decades has established that the isometric tension developed or work performed constitutes the major source of heat production. The existence of a heat of shortening and the quantification of activation heat are still under review.[35-37] In cardiac muscle older concepts relating myocardial oxygen consumption to ventricular diastolic volume[38] or "pressure

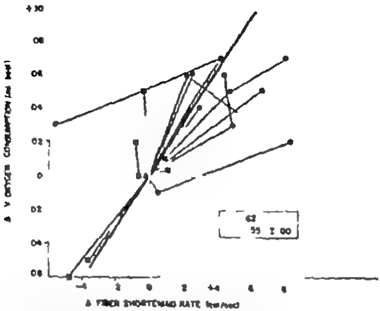


Fig. 6. Change in circumferential fiber-shortening rate is plotted against change in left ventricular oxygen consumption. Despite lack of significant correlation of the lumped data (see text) the individual increments achieve some homogeneity and statistical significance. Symbols as in Fig. 4.

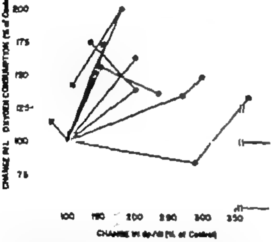


Fig. 7. Percentage change in dp/dt compared with percentage change in left ventricular oxygen consumption. Symbols as in Fig. 4. Only a directional concordance is seen.

work as opposed to "flow work,"[40] have been revised by formulations in which the development and persistence of pressure or tension were suggested as the major determinant of energy requirement.[41-43] Sarnoff[34] and Katz[38] and their collaborators have shown clearly in isolated dog hearts that oxygen requirement varied directly with the product of systolic pressure, duration of systole, and heart rate. Similar correspondence has been shown[34] in the intact dog when these hemodynamic variables were uncontrolled in response to physiological interventions such as anemia, aortic obstruction, or hypervolemia. Similarly, in the dog heart beating isobarically, isovolumetrically, or fibrillating, V_{O_2} varies depending on the tension generated.[37,38]

Work versus tension. In earlier studies, the correlation of V_{O_2} with external stroke work was poor[39,40] both in isolated muscle and in studies of intact heart in situ. The contractile element work index was suggested by Britman and Levine[22] to include the internal work performed in shortening the contractile element against the series elastic component during the isovolumic period, as well as fiber-shortening work which is reflected in external stroke work. This index showed a better correlation with V_O compared to pressure-time or force-time indices, although its improved predictive value could not be confirmed by Rolett and associates.[41]

The aforementioned studies were conducted in isolated or intact animal prepara-

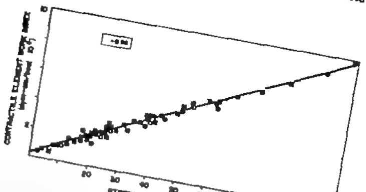


Fig 8 Comparison of stroke work with contractile element work index. The correlation is highly significant ($p < 0.001$) over a wide range of values. As noted in the text the three most discrepant values represent extremes of ventricular preload and afterload. Symbols as in previous figures.

tions and measured the effect of altering one or more hemodynamic variables while generally assuming the inotropic background to be constant (although Britman and Levine[38] did include five observations with isoproterenol). In the present study the hemodynamic variables were altered as a result of catecholamine infusion. Under these circumstances, it was frequently possible to dissociate the catecholamine effects on pressure time or force time from those on contractile element work or stroke work. Whereas in the control state all of these variables were significantly related to $\dot{V}o_2$ to a greater or lesser degree during catecholamine infusion the pressure time or force time parameters were not related at all to $\dot{V}o_2$ (Fig 3) while stroke work and contractile element work continued to be correlated to a highly significant degree (Figs. 1 *A* and 2 *A*).

Thus, whereas developed tension is the same (save for a proportionality constant of series stiffness) as contractile element work in isometric contraction work and tension may diverge during isotonic contraction. The energy requirement in this study seems related more closely to work than tension per se. This is consistent with the studies by Hill[41] and Infante and associates,[42] who found that a muscle stretched during contraction, required less energy during this zero or negative work despite development of tension.

Since ventricular pressure is a factor common to both these parameters in the intact heart, it would appear from this data that specifically accounting for the shortening of ventricular fibers at any given level of developed tension provides a significant determinant of $\dot{V}o_2$. The tension-time concept includes fiber-shortening implicitly since the duration of systole is included in the calculation and this variable may reflect stroke volume.[44] However during inotropic stimulation of the heart, the duration of systole is altered by other factors as well as particularly the rate of ventricular ejection. Thus, during phenylephrine infusion, the data diverge from the control relation between pressure time or force-time versus $\dot{V}o_2$ because at any developed load fiber shortening reflected in stroke work or contractile element work, is decreased. It is understood that the existence of the Fenn effect, about which there has been considerable question recently,[45-48] is not hereby implied.

Comparison of stroke work with contractile element work. There was no advantage in the calculation of contractile element work or power in this study compared with the simpler estimation of stroke work or power for the following reasons (1) The velocity of shortening of the contractile element and whole fiber which are reflected in the work and power produced at a given load differ only slightly and approach identity as afterload is increased; as in this study. (2) Since the contractile element work differs from stroke work only by the addition of a factor ($\bar{V}$/9 6) to the stroke volume, to account for the work done during isovolumic lengthening of the series elastic

component the two variables will be closely related particularly when stroke volume is large and ventricular volume small. (3) Also when experimental conditions induce similar directional changes of both stroke volume and ventricular volume, as for example in a Frank-Starling response to increase in ventricular volume, then relative changes in contractile element work provide little information beyond those of the stroke work. These conditions obtained frequently in the intact heart not subjected to extreme preloading or afterloading. In the present study the correlation between stroke work and contractile element work was excellent (Fig. 8) except for three points in which high preload (LVEDP 15 to 21 mm Hg) and afterloads (LVSP = 252 and 260 mm Hg) were induced. In the study by Levine and Britman, contractile element work was a better predictive index of V_O than stroke work but effects of the afterloading or preloading procedures on end-diastolic volume compared with stroke volume were not recorded. (4) The estimation of contractile element work and wall force in the heart is subject to considerable potential error. The wall thickness cavity ratio may approach 1.0 or more in systole rather than 0.1 or 0.2 as in man and the end systolic shape is even less spherical or ovoid than in man. The heuristic value of the contractile element work index is considerable and although its practical contribution to data analysis was small in the present study its relevance under other experimental conditions especially isolated or isometric preparations, or in clinical pathological states must be considered. Similar considerations apply to the concept of contractile element power.

Myocardial efficiency. The slope of the SW–V_O, or CEW–V_O relation during catecholamine infusion was somewhat less than that of the control state (Figs. 1, A and 2, A) indicating that efficiency was slightly increased or at least not decreased. In controlled experiments on animals, the effects of catecholamines on external efficiency may vary depending on initial conditions. The study of Sonnenblick and colleagues[1] in isolated dogs hearts suggested a decrease in efficiency although the small changes in ventricular end-diastolic pressure do not exclude the probability of increased fiber-shortening. On the contrary in the present study in intact dogs norepinephrine or phenylephrine did not decrease external or internal efficiency. This was true regardless of whether stroke work or contractile element work was augmented or depressed by the catecholamine. Krasnow and Sanders and their associates noted no mean change in cardiac external efficiency when human subjects or intact dogs were given isoproterenol. External efficiency calculated from the data of Yurchak and co-workers on the effects of norepinephrine in human subjects does not change significantly from control although ventricular volume probably increased. The response to muscular exercise which is at least partly mediated by the adrenergic nervous system also does not affect cardiac efficiency either in conscious dogs or human subjects. It may be therefore that when enhanced ventricular performance is allowed to express itself in increased work, no over-all change in efficiency will be noted.

It is not clear whether the extent of fiber shortening or the fiber velocity have separate effects. The corollary interpretation of the lack of marked changes in myocardial efficiency is that changes in the rate of work production that is power do not per se influence over-all energy cost. Hill noted that efficiency of frog skeletal muscle altered only minimally when power was varied significantly. Certainly the increased power developed by the intact dog heart was not clearly associated with marked changes in efficiency. However the correlations observed during norepinephrine infusion for V_O versus power were better (but not statistically significant) than for V_O versus work consistent with Sonnenblick's thesis.[1] Also the identical intercept on the V_O axis observed at zero power during all states compared with the increase in V_O at zero work with norepinephrine is consistent with the concept that velocity of fiber shortening provides a holistic determinant of myocardial V_O. Part of the difficulty in resolving effects of velocity from effects of shortening is that experimental interventions altering one frequently alter the other concomitantly. This

was observed in the present study and was inferred by Sonnenblick and associates even though end-diastolic pressure changes in their study were small. The attempt by Sanders and co-workers to separate velocity and fiber-shortening distance is difficult to interpret on the basis of the data cited.

There was no difference between norepinephrine and phenylephrine on myocardial oxygen consumption except insofar as myocardial fiber velocity and shortening were altered by the afterload or the catecholamine stimulation. These factors in turn affected work and power parameters to determine energy requirement. Norepinephrine increased myocardial oxygen by increasing fiber-shortening and fiber velocity as well as increasing ventricular force. Phenylephrine decreased myocardial oxygen consumption by decreasing fiber-shortening and fiber velocity in the face of (and as a result of) increasing ventricular force. When heart rate and developed tension are controlled, changes in velocity or extent of shortening is even more directly correlated with change in myocardial oxygen consumption than work or power. The lack of close correlation of change in $\dot{V}o_2$ with change in dp/dt (Fig. 7) was not unexpected since under conditions of changing ventricular systolic and end-diastolic pressure and heart rate dp/dt may not closely reflect changes in rate of fiber shortening. Similarly, the correlation of change in $\dot{V}o_2$ with change in fiber-shortening rate (Fig. 6) was better than might have been expected since fiber-shortening rate changes may reflect alteration in loading along a given force-velocity-length curve without change in V_{max}, as well as shifts to a new inotropic plane in the force-velocity-length relation.

Lack of myocardial anaerobiosis. There was no consistent evidence of myocardial anaerobic metabolism in the present study despite the well-known phosphorylase activation of norepinephrine in stimulating glycolysis. This concurs and amplifies other data on the absence of significant anaerobic metabolism in the heart as would be suggested by negative coronary arteriovenous differences for lactate, or shifts in the lactate-pyruvate ratio in coronary venous blood compared to the arterial or calculated excess lactate. The only exception appears to be during clinical or experimental myocardial ischemia. Thus although norepinephrine and phenylephrine have strong α-adrenergic vasoconstrictor actions including the coronary circulation, the increase in coronary perfusion pressure and the vasodilatation secondary to myocardial metabolic demand was sufficient to prevent myocardial ischemia. Indeed with both agents the increased coronary flow was accompanied by an *increase* in the coronary venous oxygen saturation. The lack of significant anaerobiosis therefore permits expression of myocardial energy requirement in terms of oxygen consumption alone.

Summary

The effects of intravenous norepinephrine and phenylephrine on myocardial $\dot{V}o_2$ of 20 intact anesthetized dogs were studied. Ventricular pressure, flow, volume, and $\dot{V}o_2$ were measured, and mean systolic force, pressure-time and force-time, fiber velocity, work and power of cardiac contraction were calculated.

The best correlation of $\dot{V}o_2$ was with power in the control state but there was also a significant correlation of $\dot{V}o_2$ with work and force parameters. This correlation remained highly significant during catecholamine infusion only for work and power, whereas the correlation with pressure-time or force-time disappeared. Stroke work correlated closely (r = 0.96) with contractile element work. Myocardial anaerobiosis did not contribute significantly to energy requirement. The mean efficiency of contraction was slightly increased by these agents. Correlation of $\dot{V}o_2$ with stroke power or contractile element power was not significantly better than the correlation with stroke work, suggesting that the net effect, if any, of fiber velocity on myocardial oxygen consumption in the intact heart is small.

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REFERENCES

1. Sonnenblick, E. H., Ross, J., Jr., Covell, J. W., Kaiser, G. A., and Braunwald, E.: Velocity of contraction as a determinant of myocardial oxygen consumption, Am. J. Physiol. 209:919, 1965.

2. Krasnow N, Rolett E. L., Yurchak P. M., Hood, W. B. Jr and Gorl R. Isoproterenol and cardiovascular performance. Am J Med. 37:514 1964
3. Krasnow N. Norepinephrine effect on myocardial oxygen consumption correlated with fiber shortening. Am J Cardiol 15 135 1965
4. Raab, W. Key position of catecholamines in functional and degenerative cardiovascular pathology. Am J Cardiol 1960 5 571 1950
5. Sarnoff S. J., Gilmore J. P., Wallace A. G., Skinner N. S., Mitchell J. H., Daggett W. M. and Mansfield, P. B. Influence of norepinephrine on myocardial oxygen consumption under controlled hemodynamic conditions. Am J Cardiol 16:217 1965.
6. Sanders, C. A., Miller R. R., and Craige E., H. B. Improvement in cardiac efficiency of techolamine-induced positive inotropy by partial beta adrenergic blockage. J Clin Invest 45 1067 1966
7. Sonnenblick E. H. Force-velocity relations in mammalian heart muscle. Am J Physiol. 202:931 1962
8. Eckstein J. W. and Abboud, F. M. Circulatory effect of sympathomimetic amines. Am Heart J 63 119 1962.
9. Aviado, D. M. J. Cardiovascular effect of some commonly used pressor amines. Anesthesiology 20 71 1959
10. Rolett E. L., Sherman, H. and Gorlin, R. Measurement of left ventricular volume by thermodilution: appraisal of technical errors. J Appl Physiol 19 1164 1964
11. Sanmarco, M. E., Fronek K., Philips, C. M. and Davila, J. C. Continuous measurement of left ventricular volume in the dog. II Comparison of washout and radiographic techniques with the external dimension method, Am J Cardiol 18:584 1966.
12. Herd, J. A., Hollenberg M., Thorburn, G. D., Kopald, H. H. and Barger A. C. Myocardial blood flow determined with krypton[85] in unanesthetized dogs, Am. J. Physiol. 203 122, 1962.
13. Zierler K. L. Equation for measuring blood flow by external monitoring of radioisotopes, Circulation Res 16:309 1965
14. Gorlin, R. and Taylor W. J. Revascularization of the myocardium by internal-mammary artery implant, New England J. Med. 275 283 1966.
15. Krasnow N., Neill, W. A., Messer J. V. and Gorlin, R. Myocardial lactate and pyruvate metabolism. J. Clin. Invest. 41:2075, 1962.
16. Burn, J. H. and Rand, M. J. Fall of blood pressure after noradrenaline infusion and its treatment by pressor agents, Brit. M. J. 1:394, 1959
17. Moss, A. J., Vittands, I. and Schenk, E. A. Cardiovascular effects of sustained norepinephrine infusion. I. Hemodynamics, Circulation Res. 18:596, 1966.
18. Holt, J. P. Estimation of the residual volume of the ventricle of the dog heart by two indicator dilution technics, Circulation Res. 4 187 1956.
19. Rapaport, E., Wiegand, B. D. and Bristow J. D. Estimation of left ventricular residual volume in the dog by a thermodilution method, Circulation Res. 11:803 1962.
20. Fry D. L., Griggs, D. M. Jr. and Greenfield, J. C. Jr: Myocardial mechanics: Tension-velocity-length relationships of heart muscle, Circulation Res. 14 73, 1964
21. Burch, G. E., Ray C. T. and Cronvich, J. A.: The George Fahr lecture—Certain mechanical peculiarities of the human cardiac pump in normal and diseased states, Circulation 5:504 1952
22. Britman, N. A., and Levine H. J. Contractile element work. A major determinant of myocardial oxygen consumption, J. Clin. Invest. 43 1397 1964
23. Huckabee W. E. Relationship of pyruvate and lactate during anaerobic metabolism. V. Coronary adequacy. Am. J. Physiol. 200 1169 1961
24. Hill, A. V. The heat of shortening and the dynamic constants of muscle. Proc. Roy Soc., London (series B) 126 136, 1938.
25. Carlson, F. D. The mechanochemistry of muscular contraction. A critical revaluation of in vitro studies, Prog Biophys. & Molecular Biol. 13 261 1963.
26. Hill, A. V. Work and heat in a muscle twitch, Proc. Roy Soc., London (series B) 136:220, 1949
27. Wilkie D. R. Heat, work and chemical change in muscle. Proc. Roy Soc., London (series B) 160 476, 1964
28. Klocke F. J., Braunwald, E., and Ross, J. Oxygen cost of electrical activation of the heart. Circulation Res. 18:357 1966.
29. Starling E. H. and Visscher M. B. The regulation of the energy output of the heart, J. Physiol. 62:243 1926.
30. Evans, C. L. and Matsuoka, Y.: The effect of various mechanical conditions on the gaseous metabolism and efficiency of the mammalian heart, J. Physiol. 49:379 1915.
31. Mc Donald, H. R., Jr: Developed tension a major determinant of myocardial oxygen consumption, Am. J. Physiol. 210:351 1966.
32. Gibbs, C. L., and Mommaerts, W. F. H. M. The heart produced and the work performed by rabbit papillary muscle, Fed. Proc. 25:518, 1966.
33. Pool, P. E. and Sonnenblick, E. H.: ATP and creatine phosphate (CP) as the energy source for myocardial contraction, Fed. Proc. 25:166, 1966.
34. Sarnoff S. J., Braunwald, E., Welch, G. H., Case R. B., Stainsby W. M. and Macruz, R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index, Am. J. Physiol. 192 148, 1958.
35. Katz L. N. and Feinberg H.: The relation of cardiac effort to myocardial oxygen consumption and coronary flow. Circulation Res. 6:656, 1958.
36. Neill, W. A., Levine, H. J., Wagman, R. J.

and Gorlin, R.: Left ventricular oxygen utilization in intact dogs: effect of systemic hemodynamic factors, Circulation Res. [illegible] 163, 1963.

37. Monroe, R. G., and French, G. N.: Left ventricular pressure volume relationships and myocardial oxygen consumption in the isolated heart, Circulation Res. 9:362, 1961.

38. Monroe, R. G., and French, G. N.: Ventricular pressure-volume relationships and oxygen consumption in fibrillation and arrest, Circulation Res. 8:260, 1960.

39. Katz, L. N., and Feinberg, H.: The relation of cardiac effort to myocardial oxygen consumption and coronary flow, Circulation Res. 6:656, 1958.

40. Fronĕk, A., and Hodlická, O.: Estimation of cardiac performance and efficiency during aortic occlusion and induced muscular activity, Circulation Res. 16:545, 1965.

41. Rolett, E. L., Yurchak, P. M., Hood, W. B., Jr., and Gorlin, R.: Pressure-volume correlates of left ventricular oxygen consumption in the hypervolemic dog, Circulation Res. 17:499, 1965.

42. Hill, A. V.: Production and absorption of work by muscle, Science 131:897, 1960.

43. Infante, A. A., Klaupiks, D., and Davies, R. E.: Adenosine triphosphate changes in muscles doing negative work, Science 144:1577, 1964.

44. Braunwald, E., Sarnoff, S. J., and Stainsby, W. N.: Determinants of duration and mean rate of ventricular ejection, Circulation Res. 6:319, 1958.

45. Wallace, A. G., Mitchell, J. H., Skinner, N. S., and Sarnoff, S. J.: Hemodynamic determinants of the duration of the phases of left ventricular systole, Circulation 26:798, 1962.

46. Hill, A. V.: The effect of load on the heat of shortening of muscle, Proc. Roy. Soc., London (series B) 159:297, 1964.

47. Mommaerts, W. F. H. M.: Energetics of muscular contraction. In Paul, W. M., Daniel, E. E., Kay, C. M., and Monckton, G., editors: Muscle, Oxford, 1965, Pergamon Press, Inc.

48. Carlson, F. D., Hardy, D. J., and Wilkie, D. R.: Total energy production and phosphocreatine hydrolysis in the isotonic twitch, J. Gen. Physiol. 46:851, 1963.

49. Ross, J., Jr., Covell, J. W., Sonnenblick, E. H., and Braunwald, E.: Contractile state of the heart characterized by force-velocity relations in variably afterloaded and isovolumic beats, Circulation Res. 18:149, 1966.

50. Krasnow, N.: Unpublished observations.

51. Gorlin, R., Cohen, L. S., Elliott, W. C., Klein, M. D., and Lane, F. J.: Effect of supine exercise on left ventricular volume and oxygen consumption in man, Circulation 32:361, 1965.

52. Coleman, H. N., III, and Sarnoff, S. J.: Effects of increasing preload on oxygen consumption in cat papillary muscle, Fed. Proc. 25:644, 1966.

53. Welch, G. H., Braunwald, E., Case, R. B., and Sarnoff, S. J.: The effect of mephentermine sulfate on myocardial oxygen consumption, myocardial efficiency, and peripheral vascular resistance, Am. J. Med. 24:871, 1958.

54. Graham, T. P., Taylor, R. R., Clingeland, H. E., Clancy, R. L., and Sarnoff, S. J.: The contribution of fiber shortening to myocardial oxygen consumption, Fed. Proc. 25:644, 1966.

55. Yurchak, P. M., Rolett, E. L., Cohen, L. S., and Gorlin, R.: Effects of norepinephrine on the coronary circulation in man, Circulation 30:180, 1964.

56. Epstein, S. E., Robinson, B. F., Kahler, R. L., and Braunwald, E.: Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man, J. Clin. Invest. 44:1745, 1965.

57. Bruce, T. A., Chapman, C. B., Baker, O., and Fisher, J. N.: The role of autonomic and myocardial factors in cardiac control, J. Clin. Invest. 42:721, 1963.

58. Khouri, E. M., Gregg, D. E., and Rayford, C. R.: Effect of exercise on cardiac output, left coronary flow and myocardial metabolism in the unanesthetized dog, Circulation Res. 17:427, 1965.

59. Hill, A. V.: The efficiency of mechanical power development during muscular shortening and its relation to load, Proc. Roy. Soc., London (series B) 159:319, 1964.

60. Wallace, A. G., Skinner, N. S., Jr., and Mitchell, J. H.: Hemodynamic determinants of the maximal rate of rise of left ventricular pressure, Am. J. Physiol. 205:30, 1963.

61. Sonnenblick, E. H.: Instantaneous force-velocity-length determinants in the contraction of heart muscle, Circulation Res. 16:441, 1965.

62. Ellis, S.: Relation of biochemical effects of epinephrine to its muscular effects, Pharmacol. Rev. 11:469, 1959.

63. Neill, W. A.: Myocardial hypoxia in patients with ischemic heart disease, Clin. Res. 14:256, 1966.

64. Krasnow, N., and Gorlin, R.: Myocardial lactate metabolism in coronary insufficiency, Ann. Int. Med. 59:781, 1963.

65. Neill, W. A.: Effects of coronary O₂ supply on myocardial aerobic and anaerobic metabolism, Fed. Proc. 24:528, 1965.

66. Aldinger, E. E., Thrower, W. B., and Darby, T. D.: Effects of several sympathomimetic amines (levarterenol, phenylephrine, and epinephrine) on coronary blood flow during cardiopulmonary bypass, S. Forum 11:161, 1960.

67. Berne, R. M.: Effect of epinephrine and norepinephrine on coronary circulation, Circulation Res. 6:644, 1958.

68. Graham, T. P., Jr., Ross, J., Jr., Covell, J. W., Sonnenblick, E. H., and Clancy, R. L.: Myocardial oxygen consumption in acute experimental cardiac depression, Circulation Res. 21:123, 1967.

Case reports

Congenital localized coronary artery aneurysm without fistula

Report of a preoperatively diagnosed case

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In comparison with coronary arteriosclerosis and thrombosis, congenital fistulas and aneurysms of the coronary vessels are rare. In earlier years, these malformations were almost exclusively found at autopsy In recent decades, however their importance has increased since it is now possible to recognize them during life and to perform surgical correction

Case report

A 55-year-old man had no family history of heart disease In childhood and adolescence his health was good Medical examination for military service revealed a cardiac murmur and he was classified as unfit He had no cardiac symptoms, however and was able to perform fairly heavy carpentering work until the age of 42 when he began to complain of breathlessness and palpitation on exertion He was then examined at another hospital. The physical findings were interpreted as indicative of mitral insufficiency or ventricular septum defect Catheterization of the right heart showed nothing abnormal. He was given lighter forms of work and for some years was fairly well Later however he became so breathless that he could scarcely walk up two flights of stairs, though walking on level ground was relatively easy Stabbing retrosternal pain occurred often on exertion and radiated out to the left axilla He had no crural edema. For the past ten years, he had been conscious of a coarse intrathoracic murmur

In March 1966 he was admitted to the University Hospital. Physical examination then revealed a man in good general health His blood pressure was 180/100 mm. Hg There was no cyanosis A precordial diastolic thrill was palpable The heart was not prolonged and there was no increased parasternal pulsation The first heart sound was split and there was a loud systolic click. The second sound was weak but was not audibly split No diastolic extra sounds were heard. In the region between the left sternal margin and the cardiac apex, a Grade II murmur (scale I to VI) was audible early in systole It had no basal continuation Early in diastole a moderately frequent Grade IV murmur was heard over the apex. This murmur was superficial The phonocardiogram tallied with the auscultatory findings (Fig 1).

Electrocardiography showed minor left intraventricular block and signs of myocardial dysfunction over the apical region but no evidence of cardiac hypertrophy (Fig 1). In a bicycle ergometer test against 800 kpm. per minute his pulse rate reached 148 beats per minute in steady state During this test, he reported diffuse sensation of intrathoracic pressure Because of this and breathlessness, the test could not be continued beyond the mentioned load The electrocardiogram (ECG) reaction during the test was normal, with no signs of coronary insufficiency The radiographic configuration of the heart was normal and the estimated volume was 490 ml. per square meter body surface

The right side of the heart was catheterized. No shunt was found and the pressures and flow were normal during rest and with a work load of 400

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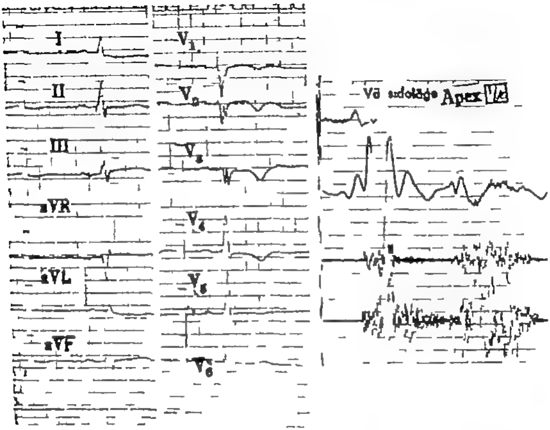

Fig. 1. Preoperative ECG (left) and phonocardiogram (PCG) over the apex (right). Paper speed 50 mm. per second for ECG, 100 mm. per second for PCG.

Fig. 2. Saccular aneurysm at the apex of the heart (arrow) filled from the dilated left anterior descending coronary artery (*LAD*) in diastole (A), in systole (B) emptying of the aneurysm.

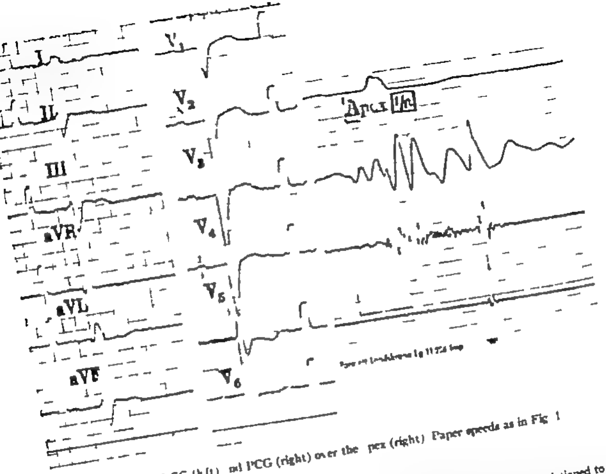

Fig 3 Postoper tn I CG (left) nd PCG (right) over the pex (right) Paper speeds as in Fig 1

kpm per minut Thorac c aortography and left ventric lar ngiogr ph were therefore performed The left de-cend ng coronary artery was tortuous and d lated nd ra l t an neurysm t the cardiac apex. The aneurys m measured pprox mately 3 by 3 cm (Fig 2) It hiled ma ly in diastole and con tracted i systole \ efferent flow was seen—the contrast medium seemed t pulsat back and fourth between the aneurysm nd the d lated coronary vessel.

Operation was performed with the aid of extra corporeal circulation. The aneurysm was found t consist of a blind sac which had narrow communication with the coronary artery The neurysm was excluded nd its communication was closed The postoperative course was complicated by cardiac tamponade during the first day and a brief episode of trial fibrillation, but otherwise was neventful.

Four months later the patient was re-examined He was much less dyspneic but still had some retro-sternal pain of indefin te type. This pain was no longer related to effort. The murmur was appreciably weaker especially in diastole (Fig 3) The ECG was nonspecifically pathologic with a somewhat prolonged ventricular complex (Fig 3). In a bicycle ergometer test, he managed 600 kpm. per minute for four minutes but was then too fatigued to con tı ue Thus, his performance was somewhat poorer than before the operation, probably because of insufficient general training Coronary angiography now showed considerable diminution i the width of the descending branch and the aneurysm was no longer visible

*This operation was performed by Dr V O. Björk.

Discussion

Considerable confusion seems to exist in the literature concerning the terms aneurysm fistula and shunt in the coronary circulation In the present discussion aneurysm denotes a more or less demarcated vascular dilatation Fistula implies an abnormal communication between two vascular regions. Shunt in this communication (the blood flow and its direction) is dependent upon the pressure gradient there.

As earlier remarked aneurysms and fistulas are uncommon in the coronary vessels. That coronary artery aneurysms do occur however has been known for a

long time. As early as 1761 Morgagni[30] described in "De Sedibus et Causis Morborum" a case of ruptured aortic aneurysm in which the left coronary artery also showed aneurysmal dilatation. This aneurysm however was of syphilitic origin. The first description of a congenital coronary aneurysm seems to have been made by Bougon in 1812.

In a review of 21 previously published cases of coronary aneurysm Steinberg and associates[36] pointed out that the aneurysm as a rule is secondary to a coronary arteriovenous fistula with shunt. This association has not always been recognized. Thus Scott[34] found that fistula had been encountered in only 5 of 48 cases of coronary aneurysm in the literature. The first of these cases was described in 1908 by Abbott.[1] Rupture of a coronary aneurysm into one of the cardiac chambers with resultant secondary fistula was reported by Minder.[29] The accuracy of Steinberg's statement is borne out by our own observation that the relatively numerous cases of coronary artery aneurysm published in recent years seem all to have been associated with fistula. The literature now contains about 100 cases of coronary aneurysm but the frequency of coexistent fistula cannot be exactly stated. This total includes seven cases of coronary arteriovenous fistula previously reported from Uppsala University Hospital.[7]

Scott[33] classified the aneurysms as diffuse or localized. The diffuse aneurysms were always congenital. The localized aneurysms could be congenital, but could also be secondary to arteriosclerosis, syphilis, septic emboli, or periarteritis nodosa.

The embryology of these malformations has been discussed by many writers.[10,1,18,21,25,28] They are presumed to be caused by one of three mechanisms. The normal development of the coronary vessels may be inhibited with retention of the primitive sinusoids in the myocardium. These sinusoids consist of blood filled intertrabecular cavities which communicate with the developing coronary vessels and the cardiac chambers. Normally they disappear but embryologic and autopsy studies have shown that persistence of sinusoids may give rise to both aneurysm and fistula. Our case presumably belonged to this group. Also at a later stage of development an anomalous communication may arise between the branching coronary arteries and veins and a secondary aneurysm may form from the fistula. In contrast to the more primitive sinusoids, these fetal vessels distinctly resemble the fully developed arteries and veins. A third type of arteriovenous fistula occurs from vessels with anomalous origin from the pulmonary artery or the right side of the heart. These vessels may anastomose with coronary arteries and produce a fistula with shunt.

Congenital coronary aneurysms, with or without fistula, mainly involve the right coronary artery, whereas the acquired aneurysms are predominantly left-sided.[12,33] In this connection it is pertinent that aneurysm of the sinus of Valsalva is also commonest in the right sinus.[38] Fistulas from coronary arteries usually run into the right side of the heart, including the pulmonary artery. The percentage ratio of right-left cardiac entry has been stated as 90:10.[24,25]

The ages of the cases of coronary artery aneurysm with or without fistula in the literature range from 14 months to 87 years. A male:female ratio of 14:1 has been reported. Frequently the aneurysm was an adventitious finding in a clinically symptom free patient. The common symptoms are those of decompensation such as dyspnea and thoracic pain. Such symptoms probably are secondary to the shunt. Valdivia and associates[39] for example reported the case of a 25-year-old man with gross cardiac enlargement who died of cardiac failure. Although an exploratory thoracotomy had been performed a shunt between the right coronary artery and the right atrium was first discovered *post mortem*. In rare cases, rupture of the aneurysm has been fatal.[27] Other reported complications are myocardial ischemia and infarction[12,26] and endocarditis.[21]

At auscultation the most conspicuous finding when fistula is present is a precordial, usually continuous murmur.[10,11] As a rule the murmur is heard to the left of the sternum and towards the base of the heart and it is coarse and superficial. Sometimes however the murmur is audible only in systole and in other locations.[2] The available literature contains no case

of nonfistulated coronary artery aneurysm with a murmur. The continuous precordial murmur may be confused with the murmur in a number of other disorders (Table I). In our case the dominant and superficial nature of the murmur in diastole gave rise to the suspicion of fistula between a coronary artery and the left ventricle when a gradient may be expected in diastole.

The cardiac outline on plain radiograms may be normal, as in our case, or it may be enlarged or otherwise altered. Intracardiac calcifications, lying within the aneurysm, have also been observed. Coronary angiography, first performed in 1952,[20] will reveal the aneurysm and fistula. Demonstration of coronary arteriovenous shunt by catheterization was first described by Walther and co-workers. Our patient had a localized aneurysm without shunt and catheterization of the right heart showed nothing abnormal.

Contrary to what might be expected, electrocardiographic changes indicative of coronary insufficiency are uncommon, if one excepts cases with an anomalous coronary artery originating from the pulmonary artery. If due to shunt a fistula with fairly large flow remains patent for a sufficiently long time, hypertrophy of one or both ventricles may develop and will then be reflected in the ECG tracings. In our case the preoperative ECG was nonspecifically pathologic with negative T waves over the anteroapical region of the left ventricle. The patient's response to the bicycle ergometer test contradicted coronary insufficiency. The ECG changes presumably were attributable to the size and site of the aneurysm.

Although many cases in the literature reached a high age and were asymptomatic, the mentioned risks of complications constitute indications for surgical correction of congenital coronary artery aneurysm. The number of surgically treated cases is rapidly increasing. Hitherto, about 40 such cases have been reported with three deaths in the immediate postoperative period. In our case operation was further warranted by the gradual preoperative deterioration.

Table I. Some conditions which may cause a continuous precordial murmur (From Cullhed, Bjork, and Bjork: Am. Heart J. 64:111, 1962)

I. Intrathoracic
- A. Cardiac
  1. Ruptured aneurysm of sinus of Valsalva
  2. Ventricular septal defect with aortic or pulmonary regurgitation
  3. Coronary artery fistula and/or aneurysm
  4. Aortic stenosis and regurgitation
- B. Extracardiac
  1. Patent ductus arteriosus
  2. Aorticopulmonary septal defect
  3. Pulmonary arteries with bronchial-pulmonary anastomoses
  4. Peripheral pulmonary stenosis, single or multiple
  5. Coarctation of aorta with collaterals
  6. Ruptured aortic aneurysm
  7. Arteriovenous shunt
     - Pulmonary
     - Systemic
     - Systemic-pulmonary
  8. Lactating mamma
  9. Sternal marrow metastases

II. Extrathoracic (transmitted)
- Venous hum from the neck or rarely the abdomen
- Arteriovenous shunts

Summary

The case of a 55-year-old man with an apical coronary artery aneurysm is presented. The aneurysm was in communication with the dilated descending branch of the left coronary artery. There was no shunt. The physical findings suggested aneurysm with a fistula to the left ventricle. Coronary angiography demonstrated a localized aneurysm in the wall of the left ventricle but no fistula. The aneurysm was surgically obliterated and the patient made a good recovery. This seems to be the first described case of coronary artery aneurysm without fistula to be fully diagnosed prior to surgical exploration.

REFFRENCES

1. Abbott, M. E.: Anomalies of the coronary arteries, in Osler, W., editor: Modern medicine, ed. 1, Philadelphia and New York, 1908, Lea & Febiger Publishers, p. 420.
2. Abrams, L. D., Evans, D. W., and Howarth, F.: Coronary artery—right ventricular fistula treated surgically, Brit. Heart J. 29:132, 1967.
3. Alexander, S., and Green, H.: Coronary blood

vessel arising from cardiac ventricle, Arch. Path 53 187 1952.
4. Bellet, S., and Gouley B. Congenital heart disease with multiple cardiac anomalies, Am. J M Sc. 183:458, 1932
5. Belaky H., Scharnoff G., and Gilbert, S. Aneurysm of coronary artery New York J Med 55 3151 1955
6. Björck, G and Crafoord, C. Arteriovenous aneurysm of the pulmonary artery simulating patent ductus arteriosus Botalli, Thorax 2:65, 1947
7. Björk, V O and Björk, L. Coronary artery fistula, J Thoracic & Cardiovas. Surg 49:921 1965
8. Bougon, M Observation sur une anévrisme d'une des artères coronaires ou cardiaques, Bibliothèque Méd. 37:85 1812, Quoted by Packard and Wechler[27]
9. Bosher L., Vasli, S. McCue, C., and Belter L. Congenital coronary arteriovenous fistula associated with large patent ductus, Circulation 20:254 1959
10. Carmichael, D and Davidson, D Congenital coronary arteriovenous fistula, Am. J Cardiol 8:846, 1961
11. Colbeck, J and Shaw J Coronary aneurysm with arteriovenous fistula, Am Heart J 48:270, 1954
12. Cdlhed, I Björk, L., and Björk, V O Congenital pericardial arteriovenous fistula, Am. Heart J 64 111 1962.
13. Edwards, J Gladding, T and Weir A J Congenital communication between the right coronary artery and the right atrium J Thoracic Surg 35:662, 1958.
14. Fell, E., Weinberg, M Gordon H., Gasul, B and Johnson, F Surgery for congenital coronary artery arteriovenous fistula, Arch. Surg 77 331 1958
15. Gasul, B Arcilla, R A Fell, E Lynfield, J Bicoff J and Luan, L. Congenital coronary arteriovenous fistula, Pediatrics 25:936 1961
16. Grant, R. Development of the cardiac coronary vessels in rabbit, Heart 13:261 1926
17. Grant, R and Regnier M. The comparative anatomy of the cardiac coronary vessels, Heart 13:285 1926.
18. Grant R., and Wilson, J A case of congenital malformation of the heart in an infant associated with partial heart block, Heart 12:295 1926
19. Halpert, B. Arteriovenous communication between the right coronary artery and the coronary sinus, Heart 15 129 1930.
20. Knobblich, R., and Rawson, A. Arteriovenous fistula of the heart, Am Heart J 52:474 1956.
21. Lowitt, W J and Lutz, S., J Embryological aneurysm of the myocardial vessels, Arch. Path. 57:63 1954
22. Minder W Aneurysma congenitum coronariae Cardiologia 22:35 1953
23. Morgagni, J B De sedibus et causis morborum, Venetiis, 1761, Quoted by Munkner and co-workers[24]
24. Munkner T Petersen, O and Vesterdal, J Congenital aneurysm of the coronary artery with an arteriovenous fistula, Acta radiol 50:333, 1958.
25. Nadas, A. Pediatric cardiology, ed. 2 Philadelphia and London, 1963 W. B. Saunders Company p 511
26. Neufeldt, H., Lester R., Adams, P Anderson, R., Lillehei, C and Edwards, J Congenital communication of a coronary artery with a cardiac chamber or the pulmonary trunc, Circulation 24:171 1961
27. Packard, M and Wechler H Aneurysm of the coronary arteries, Arch. Int. Med. 43:1 1929
28. Scott, D Aneurysm of the coronary arteries, Am Heart J 36:403 1948
29. Soloff L Anomalous coronary arteries arising from the pulmonary artery Am. Heart J 24 118, 1942
30. Steinberg I Baldwin, J and Dotter C. Coronary arteriovenous fistula, Circulation 17:372, 1958
31. Trevor R. Aneurysm of the descending branch of the right coronary artery Proc. Roy Soc. Med. 5:20, 1911
32. Upshaw C. Congenital coronary arteriovenous fistula. Report of a case with analysis of seventy three reported cases, Am. Heart J 63:399 1962
33. Valdivia, E Rowe, G., and Angevine, D Large congenital aneurysm of the right coronary artery Arch. Path. 43:168, 1947
34. Walther R Starkey G., Zervopolus, E and Gibbons, G Coronary arteriovenous fistula, Am J Med. 22:213 1957

Transient systolic murmurs in angina pectoris

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Mitral incompetence due to papillary muscle dysfunction is well recognized as a complication of myocardial infarction Burch and his colleagues[3] also suggested that ischemia of the papillary muscles in angina pectoris might similarly cause mitral incompetence The following two cases appear to demonstrate this phenomenon

Case reports

Case 1 I 1956 R P 41 year-old male accountant, developed angina. H had no history of rheumatic fever Physical examination revealed blood pressure of 175/115 mm Hg His electrocardiogram (ECG) showed a small R wave In V and T wa inversion I Leads V In 1960 four years later he was referred for surgical treatment beca se of almost total incapacity from angina. On examination while he had ischemic pain, n pical Grade 4/6 ejection syst lic murmur and soft mid-diastolic murmur were found both disappeared w thi five minutes of relief of his angina. Although an ECG taken with the patient at rest was normal hanges of nterolateral ischemia developed on exertion In December 1960 when the left sympathetic hain from T1-6 was removed, calcification was noted in the terior descending branch of the left coronary artery The surgical treatment produced only a transient improvement and in 1964 the patient became aware of a rasping noise in his chest whenever he developed angina. It was then observed that an apical systolic murm (Grade 4/6 crescendo-decrescendo) became audible during attacks of nginal pain. This radiated over the whole precordium and into the axilla. Electrocardiography during nginal ttacks showed symmetrical T wave inversion nd S-T depression in Lead II III aV nd the left precordial leads (Fig 1). The hemoglobin total and differential wh t cell count, sedimentation rat serum proteins, electrolytes, urea, transaminases and cholesterol were norm l, a were chest radiography and cardiac screening Angiocardiographic studies following the injection of contrast medium into the pulmonary artery showed no left atrial filling defect. During ngiography the patient developed a transient ventricular tachycardia nd further studies were therefore not pursued Apex phonocardiographic recordings before nd after two minutes of gentle exercise (and when pontaneous angina occurred) showed that the murmur developed with the onset of angina nd disappeared his two minutes of hewing 0 6 mg glyceryl trinitrate (Fig 2).

Case 2 E. C a 72-year-old park keeper was adm tted on M y 29 1967 because of the sudden onset of severe breathlessness. He had had bronchitis for ma y years and gave history of rheumatic fever at the age of 20 In February 1967 when he was hospitalized because of a exacerbation of his bronchitis, examination of his heart showed no bnormality

H was sweating and orthopneic upon examination. The pulse was regular t a rate of 120 beats per minute, his blood pressure was 150/90 mm. Hg and there were signs of pulmonary edema The apex beat was not palpable, but the heart sounds were normal and no bruit was aud ble An ECG showed sinus tachycardia and left is deviation. H condition improved after treatment with intravenous digoxin frusemide and minoph lline.

Four d ys later he developed severe central chest pain and the changes of acute posterolateral

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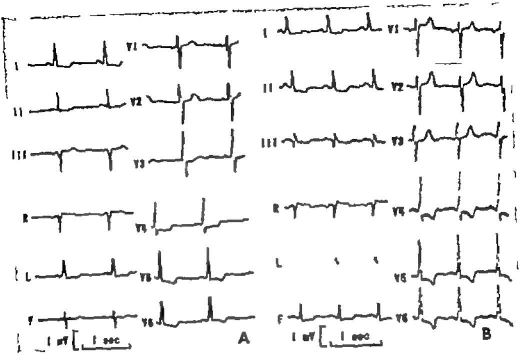

Fig. 1. R. P. twelve lead ECG taken *A* while pain free and *B* during an episode of angina.

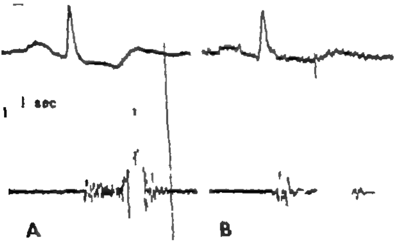

Fig. 2. R. P. apex phonocardiogram recorded *A* during angina and *B* when pain free. (N. E. P. Audiofrequency amplifier A 642. ECG Lead II.)

infarction appeared in the ECG (Fig. 3). Two days later a prolonged P-R interval appeared. The white cell count, sedimentation rate, transaminases, and lactic dehydrogenase all increased. A gallop rhythm became audible and the heart on x-ray was seen to be dilated. A pericardial friction rub was never heard.

In the next three weeks the patient was maintained at rest in bed and experienced episodes of angina followed by acute pulmonary edema. In these, he was noted to develop a Grade 4/6 apical ejection systolic bruit and a short apical mid-diastolic bruit. If he was given trinitrin as soon as he developed pain, breathlessness and the clinical

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signs of pulmonary edema did not develop. The apical bruit partly disappeared. An apex phonocardiogram between and during attack of angina is illustrated in Fig 4. Chest screening showed no evidence of ventricular aneurysm or paradoxical pulsation and no visible dilatation during angina. Four weeks after the infarct he had some dyspnea on exertion and a soft late systolic bruit but the physical and radiological signs of pulmonary edema had disappeared.

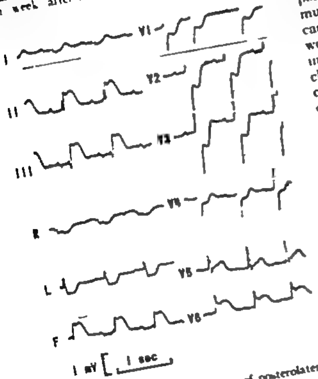

Fig 3 E. C. ECG taken at time of posterolateral infarction

Discussion

In many cases myocardial infarction involves the papillary muscles of the left ventricle. DePasquale and Burch reported gross scars or infarction of these muscles in 25.2 per cent of 420 autopsy cases but as all but one of these patients were male this may not reflect the over-all incidence. Ischemic damage to these muscles may result in their rupture, in rupture of the attachments of the chordae tendineae or in failure of an adequate contraction causing persistent mitral incompetence. In the two patients described neither the papillary muscles nor their chordae tendineae could have ruptured as the murmurs were transient.

Opinions vary concerning the nature of the regurgitant murmur associated with papillary muscle dysfunction. According to Burch and associates it is mid systolic and diamond shaped in quality with an interval between the first heart sound and the onset of the murmur. Tavel and colleagues and Barlow and Bosman concur with this description while others consider the murmur to be pan-systolic or diamond shaped and pan systolic. Heikkila also states than an ejection

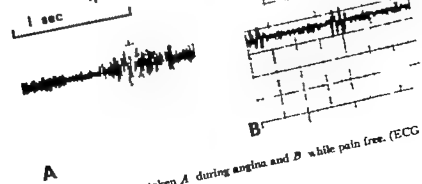

Fig 4 E. C., apex phonocardiogram taken A during angina and B while pain free. (ECG Lead III.)

murmur may change to a high frequency pan-systolic type during severe angina. In both our patients, the murmur was undoubtedly pan-systolic but its diamond quality was apparent in late systole in the first patient and in mid systole in the second (see Figs. 2 and 4).

Burch and his colleagues[3] considered that the ischemic papillary muscles can hold the mitral cusps together during the phase of isometric contraction but they may later fail to shorten with the general bulk of ventricular muscle and so allow regurgitation at the mitral valve. The insufficiency increases during contraction and the murmur is thus ejection in type. Mitral incompetence has been confirmed by cineangiography in several reported cases[4,11,12] and the condition corrected by mitral valve replacement in three of these.[12]

Edwards and Burchell[5] and Levy and Edwards[8] state that in the dilated left ventricle the bases of the two papillary muscles are further apart than normal. The chordae tendineae normally pass vertically (with respect to the inflow channel) from the tips of the papillary muscles to valve cusps. Dilatation of the ventricle changes the normal chordal direction from vertical to horizontal allowing inadequate opposition of the valve leaflets and causing mitral incompetence.

In our first case the heart was of normal size and there was no evidence of left ventricular dilatation during anginal attacks. His ECG showed changes similar to those described by Phillips and associates[11] as suggestive of anterolateral papillary muscle infarction, namely marked depression of junction J in the middle to left precordial leads associated with convexity upward deformity of the ST-T interval. These changes became more marked during angina (Fig. 1). It is therefore highly likely that his incompetent murmur was a result of transient papillary muscle ischemia.

In the second patient the pain and murmur were almost always followed by the development of acute pulmonary edema. Although there was some cardiac dilatation screening showed no evidence of paradoxical pulsation or ventricular aneurysm and the left atrium was not enlarged. One cannot, however, exclude with certainty the possibility of acute ischemic dilatation of the left ventricle contributing to the mitral incompetence. Atrial fibrillation, atrial flutter, and multiple ventricular extrasystoles were detected transiently during his illness, but at the time when an electrocardiographic record was obtained during episodes of pain and pulmonary edema his rhythm was of sinus origin.

Free leakage into a small left atrium and resultant pulmonary edema occur when mitral incompetence appears suddenly because of disruption of the valve apparatus.[12] This patient's pulmonary edema is thought to have been caused in this way. He probably now has some persistent papillary muscle damage causing a permanent bruit.

Summary

Two patients are described in whom a systolic diamond shaped murmur appeared during episodes of angina pectoris. This is thought to be due to papillary muscle dysfunction during periods of ischemia.

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REFERENCES

1. Barlow, J. B., and Bosman, C. K.: Aneurysmal protrusion of the posterior leaflet of the mitral valve: An auscultatory-electrocardiographic syndrome, Am. Heart J. 71:166, 1966.
2. Bashour, F. A.: Mitral regurgitation following myocardial infarction. The syndrome of papillary mitral regurgitation, Dis. Chest 48:113, 1965.
3. Burch, G. E., DePasquale, N. P., and Phillips, J. H.: Clinical manifestations of papillary muscle dysfunction, Arch. Int. Med. 112:112, 1963.
4. DePasquale, N. P., and Burch, G. E.: Necropsy incidence of gross scars or acute infarction of the papillary muscles of the left ventricle, Am. J. Cardiol. 17:159, 1966.
5. Edwards, J. E., and Burchell, H.: Pathological anatomy of mitral insufficiency, Proc. Staff Meet. Mayo Clin. 33:497, 1958.
6. Fluck, D. C., Taubman, J. O. T., Cleland, W. P., and Mounsey, J. P. D.: Acute mitral incompetence after acute myocardial infarction with successful early treatment by mitral valve replacement, Lancet 2:1051, 1966.

7. Heikkila, J.: Mitral incompetence complicating myocardial infarction, Brit. Heart J. 29:162, 1967.
8. Levy, M. J., and Edwards, J. E.: Anatomy of mitral insufficiency, Progr. Cardiovas. Dis. 5:119, 1962.
9. Orlando, M. D., Wooley, C. F., Scarpelli, D., and Ryan, J. M.: Mitral regurgitation caused by infarcted papillary muscles. Report of 15 cases, Circulation Suppl. III:136, 1964.
10. Phillips, J. H., Burch, G. E., and DePasquale, N. P.: The syndrome of papillary muscle dysfunction, Ann. Int. Med. 59:508, 1963.
11. Phillips, J. H., DePasquale, N. P., and Burch, G. E.: ECG in infarction of the anterolateral papillary muscle, Am. Heart J. 66:339, 1963.
12. Raftery, E. B., Oakley, C. M., and Goodwin, J. F.: Acute subvalvular mitral incompetence, Lancet 2:360, 1966.
13. Tavel, M. E., Campbell, R. W., and Zimmer, J. F.: Late systolic murmurs and mitral regurgitation, Am. J. Cardiol. 15:719, 1965.

Metabolism of the heart in health and disease. Part I*

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Some of the major advances in cardiology are now taking place in the field of biochemistry. The metabolism of the normal heart is better understood, and the mechanisms whereby the heart adapts to oxygen lack, tissue death, and overwork have all been studied at a cellular level. There have been corresponding advances in the understanding of the metabolism of the heart in fatty infiltrations, ischemic heart disease, and congestive heart failure.

In this review, the biochemical advances relevant to the understanding of the metabolism of the diseased heart have been selected. Special emphasis has been placed on the following: (1) glucose and glycogen metabolism, which are especially important in the response to oxygen lack; (2) lipid metabolism and its derangements in pathological states; (3) myocardial oxidative metabolism and the interaction between carbohydrate and lipid metabolism; (4) protein synthesis, which is of importance in the adaptation of the heart to hypertrophy and failure; (5) the metabolism of calcium, which controls contractility and may play a role in heart failure; (6) the influence of the catecholamines on contractile force and metabolism of the normal and the failing heart; and (7) metabolism of the heart in endocrine and nutritional cardiopathies and in infarction.

Coverage of many other aspects of heart metabolism is provided by the publications of Bing,[2] Stewart and associates,[3] and Evans. Bing has already fully discussed the impetus that studies with coronary sinus catheterization have given to the understanding of human myocardial metabolism both in his Harvey Lecture[1] and in a recent review. Earlier work, done chiefly on the isolated frog heart or the dog heart-lung preparation, has been reviewed by Cruickshank[4] and Lovatt Evans.

This review is intended primarily for physicians and cardiologists, and others whose interests encompass both biochemical and clinical aspects of heart metabolism. It is recognized that some basic scientists may regard the presentation and conclu-

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Chemical abbreviations used:

ATP	= adenosine-5'-triphosphate
ADP	= adenosine-5'-diphosphate
AMP	= adenosine-5'-monophosphate
Pi	= inorganic phosphate
Cyclic AMP	= cyclic adenosine-3',5'-monophosphate
CrP	= creatine phosphate or phosphocreatine
NAD and $NADH_2$	= oxidized and reduced forms of nicotinamide-adenine dinucleotide (formerly DPN and $DPNH_2$)
NADP and $NADPH_2$	= oxidized and reduced forms of nicotinamide-adenine dinucleotide phosphate (formerly TPN and $TPNH_2$)
FFA	= free fatty acids or unesterified fatty acids or nonesterified fatty acids (NEFA)
TGFA	= triglyceride fatty acids
G-6-P	= glucose-6-phosphate

*Parts II and III will appear in forthcoming issues of this Journal. A complete list of references will appear after Part III. This review only refers to literature received by Feb. 29, 1968.

sions as oversimplified but some simplification is the inevitable price of any attempt to bridge the gulf between basic scientific work and the clinical application of such work.

I. Control of glucose uptake and glycolysis

Importance of glucose for metabolism of the heart. Glucose is a myocardial substrate of special historical, biochemical, and pharmacological interest. Historically, interest in glucose metabolism dates back to at least 1907 when Locke and Rosenheim found glucose uptake in the isolated heart preparation of Langendorff. In 1912 Knowlton and Starling found that sugar was used by the dog heart and that pancreatectomy impaired this power of consuming sugar. Evans, in 1914 suggested that only one-third of the heart's energy is supplied by carbohydrate oxidation. Cruickshank and his associates suggested that direct combustion of fat, probably the blood fatty acids, met the rest of the heart's energy requirements. Thus, these early workers delineated carbohydrate and fatty acids as 2 of the most important myocardial fuels. From the biochemical point of view glucose is of interest because factors controlling its uptake and utilization by glycolysis or glycogen synthesis have been extensively studied and an integrated scheme of the control of these processes is now being established. Pharmacologically glucose is of interest because of the possible use of glycolysis in maintaining anaerobic metabolism. Furthermore the use of glucose solutions has been proposed in the therapy of various forms of heart disease.

Regulation of glucose uptake and phosphorylation in isolated heart tissue. In the isolated perfused rat heart, the rate of glucose uptake from the perfusate into the heart cells plays an important role in the regulation of subsequent intracellular glucose utilization. Glucose uptake is limited by the rate of transport of glucose across the cell membrane, a process thought to involve a stereoscopic glucose carrier. The increased glucose uptake by the perfused heart when insulin is added to the medium is explained by acceleration of membrane transport and in these circumstances, the rate of membrane transport exceeds the rate of phosphorylation of intracellular glucose and phosphorylation becomes limiting for glucose uptake.

It should be stressed that the isolated rat heart preparation contains tissue-bound insulin on removal from the body and that either the administration of insulin-antiserum to the donor rat or a preperfusion of about 30 minutes is required to reduce sugar transport to a basal state. The longer preperfusion period used by Williamson may explain why he found a lower basal glucose uptake and a greater insulin effect than did Morgan and co-workers.

Acceleration of the rate of membrane transport also occurs during anoxic perfusion or when the heart work is increased; in either case membrane transport remains rate-limiting. These findings show that in a variety of conditions, membrane transport is an important step in the control of glucose utilization.

Glucose phosphorylation is measured by subtracting the intracellular glucose from the glucose uptake on the assumption that all glucose taken up by the heart is phosphorylated unless it accumulates within the cells. Phosphorylation is decreased in the hearts from alloxan-diabetic rats and during the addition of ketone bodies or palmitate to a perfusion medium containing glucose and insulin. Conversely, anoxia and muscular work accelerate phosphorylation.

Attempts have been made to relate hexokinase activity to changes in the content of G-6-P, which inhibits both particulate and soluble forms of semipurified heart muscle hexokinase. The G-6-P content may in turn be regulated by phosphofructokinase activity which is decreased in diabetes and accelerated by anoxia and muscular contraction. This sequence would accentuate the importance of the postulated control of phosphofructokinase in the regulation of glucose utilization. However there is no correlation between the G-6-P content of the frog muscle or of the heart and hexokinase activity when glucose uptake and glycolysis are stimulated by insulin, glucagon, epinephrine, ouabain, or muscular work, or when glycolysis is inhibited by acetate

and pyruvate.[28] One factor explaining this discrepancy might be the content of Pi which relieves G-6-P inhibition of heart mitochondrial hexokinase.[37] Another factor is the ever present problem of relating the concentration of a substance actually available to the enzyme to the over-all mean cellular level of that substance. It is, however, apparent that control of hexokinase in the heart requires further study.

Regulation of glucose uptake and phosphorylation in the heart in situ. The question arises whether the above control mechanisms proposed as a result of studies in the isolated heart and subcellular systems are strictly relevant to the heart in situ. For example, glucose is taken up by the isolated perfused rat heart even at very low circulating glucose concentrations, such as 15 to 23 mg. per cent.[20] This finding contrasts with the glucose "threshold" which prevents glucose uptake by the human or dog heart in situ below an arterial concentration of about 60 mg. per cent.[40-42] The threshold falls to about 10 mg. per cent when insulin is administered to dogs, while the threshold is abnormally high in untreated diabetic dogs and diabetic humans.[42, 43] A simple possible explanation for the glucose threshold is that it is the result of the uptake of substrates other than glucose by the heart in situ. For example, a severe diabetic state is associated with increased circulating concentrations of FFA and ketone bodies, which decrease the myocardial glucose uptake[31, 42, 44] and could thereby create an apparent threshold for glucose uptake. Conversely, the administration of insulin is associated with a decreased circulating FFA concentration which might lower the apparent glucose threshold.

Although the kinetics of glucose uptake by the dog heart in situ are consonant with the carrier mechanism described for the isolated rat heart, there appear to be important kinetic differences[42] which need further confirmation.

An intravenous infusion of glucose into man or the dog is followed by an increased myocardial glucose uptake, but an infusion into the coronary artery does not result in any sustained increase of the glucose uptake by the heart in situ.[40-42, 45] These observations suggest (1) that the uptake of glucose by the heart in situ is inhibited by factors operating even when the arterial glucose concentration exceeds the threshold value and (2) that these factors are at least partially overcome during an intravenous glucose infusion, when release of insulin and decrease of the circulating FFA concentration could encourage glucose uptake. Insulin acts on the dog heart in situ by increasing the rate of membrane transport to exceed the phosphorylation rate,[42] as also occurs in the isolated rat heart.

The possible inhibition of the phosphorylation of intracellular glucose by the myocardial level of G-6-P has been studied in the dog heart in situ during the administration of insulin and epinephrine; however, as in the isolated rat heart, there is insufficient evidence to accept a simple inverse relationship between the phosphorylation rate and the G-6-P content.[77, 42]

Thus, it appears that the basic patterns of control of glucose uptake and phosphorylation delineated in the isolated rat heart may, at least to some extent, be reconciled with observations on the heart in situ. This suggestion appears to be supported by the findings that the rates of glucose uptake and phosphorylation found in the dog heart in situ are of the same order of magnitude as in the isolated rat heart at comparable circulating glucose concentrations.[42] The G-6-P level in the dog heart in situ varies from values similar to those found in the isolated rat heart[77, 44] to much lower values.[46] However, such comparisons may be entirely fallacious because of the multiplicity of ill-understood factors affecting glucose uptake in vivo. Until further information is available, it may be assumed that the over-all pattern of control of glucose metabolism delineated in the isolated perfused rat heart is applicable to the intact heart in situ, but only further studies will show whether the control processes are the same in detail.

Glycolysis: role of phosphofructokinase. Glycolysis is here defined as the processes

*Throughout this review the term "level" is used to express the measured tissue content of a substance, in terms of micromoles per gram of whole tissue, whereas "concentration" means the chemical concentration in micromoles per liter of cellular or extracellular water.

by which G-6-P is converted to pyruvate. Because of the absence of glucose 6-phosphatase in the heart G-6-P must be utilized by entering pathways of either glycolysis or glycogen synthesis. When glycolysis in the perfused rat heart is increased by anoxia the concentrations of G-6-P and fructose 6-phosphate decrease while the concentration of fructose 1 6-diphosphate increases. This is evidence for control by phosphofructokinase because there is no detectable fructose diphosphatase activity in the heart muscle. The properties of highly purified phosphofructokinase from the guinea pig heart have shown that as in many other tissues and species, the enzyme is strongly inhibited by one of its substrates, ATP the inhibition is relieved by cyclic AMP AMP and Pi. Another substrate fructose 6-phosphate and both products of the reaction (ADP and fructose 1 6-diphosphate) also relieve ATP inhibition. In isolated heart tissue deprived of oxygen a threefold increase of AMP and Pi concentrations can account for the increased phosphofructokinase activity. However changes other than those in adenine nucleotides must be invoked to account for changes in the glycolytic flux in states of enhanced fatty acid oxidation and in changes of pH.

During perfusion of the isolated heart with fatty acids or ketone bodies, or in the hearts of alloxan-diabetic or starved rats, the citrate concentration increases several fold. Citrate in physiological concentrations inhibits phosphofructokinase in vitro and it is thought in the perfused rat heart. Thus, phosphofructokinase is highly sensitive to inhibition by 2 end products of aerobic glycolysis, ATP and citrate.

pH is also involved in the regulation of muscle phosphofructokinase. When isolated frog skeletal muscle is repetitively stimulated CrP breakdown results in its becoming alkaline before subsequent lactate accumulation causes acidity. The rise of pH appears to relieve ATP inhibition of phosphofructokinase activity. A similar mechanism may explain the increased glycolysis at high medium pH values in the isolated perfused rat heart.

Glycolysis other control points Bücher and Russman have reviewed glycolysis from the point of view of a series of reactions some of which are maintained close to equilibrium while others deviate from equilibrium. From the profile of glycolytic intermediates in the isolated rat heart Williamson[17] finds 3 nonequilibrium reactions phosphofructokinase glyceraldehyde phosphate dehydrogenase and pyruvate kinase. Phosphofructokinase deviates most from equilibrium which is consonant with its accepted major role in the control of glycolysis. Control passes transiently from phosphofructokinase to glyceraldehyde-P dehydrogenase during epinephrine stimulation and to pyruvate kinase during anoxia.

Pentose shunt activity Using the relative rates of CO_2 formation from glucose labelled in positions 1 or 6 as a guide the pentose (hexose monophosphate) shunt is judged to be either quiescent or only moderately active in normal heart tissue. Furthermore the in vitro activity of G-6-P dehydrogenase a key enzyme in the pentose shunt is low when compared with that of phosphofructokinase, the key enzyme in the direct glycolytic pathway. G-6-P dehydrogenase activity may be further limited by availability of NADP in the heart. The shunt is considerably more active in the fetal heart in keeping with the greater requirements for ribose for protein and lipid synthesis in the fetus. A rapid increase of pentose shunt activity (within 5 hours) is also found in association with the increased protein and lipid synthesis during the reparative processes following myocardial infarction. There is also an increase in the overloaded failing guinea pig heart lung preparation. Thus, the pentose shunt is normally relatively inactive but can rapidly increase its activity when synthetic processes are accelerated.

Fates of pyruvate In anoxia pyruvate forms lactate rather than entering the citrate cycle but the reason for this is not fully known. Accumulation of NADH required for conversion of pyruvate to lactate may inhibit pyruvate dehydrogenase activity. Another factor involved might be the level of intracellular pyruvate which decreases from 15 to 10 μM immediately after the onset of anoxia in the isolated rat heart. Heart pyruvate dehy

drogenase has K_m for pyruvate of 21 μM[83] hence the decrease in anoxia could cause a substantial slowing of dehydrogenation. In fatty acid respiration, pyruvate dehydrogenase activity is inhibited by accumulation of acetyl CoA and NADH[67, 4] with a decrease in the rate of pyruvate entry into the citrate cycle.[70] Thus, either in anoxia or in fatty acid respiration, pyruvate dehydrogenation is decreased.

The rate of conversion of pyruvate to lactate may be controlled by the properties of lactate dehydrogenase. Detailed studies of the incidence and properties of lactate dehydrogenase isoenzyme by Kaplan and co-workers[71, 72] have suggested that the M isoenzyme is present mainly in the muscle that can function anaerobically and the H isoenzyme in the muscle that functions only aerobically (such as the heart). The H isoenzyme is inhibited by pyruvate and is suggested that this ensures pyruvate entry into the citrate cycle during conditions of increased glycolytic flux. On the other hand the M isoenzyme is less sensitive to pyruvate inhibition, which would allow conversion of pyruvate to lactate with consumption of extramitochondrial NADH and maintenance of anaerobic glycolysis. This postulated role of pyruvate inhibition has been criticized because the pyruvate concentrations found in the muscle in vivo do not approach those required to inhibit the enzyme in vitro.[73] Another criticism of the suggested role of substrate inhibition is that, in the perfused rat heart, an increase of circulating pyruvate concentration from 2.5 to 10 mM actually doubles the lactate output.[79] In these conditions, the intracellular pyruvate concentrations very probably exceed those reached during glycolysis, but lactate dehydrogenase does not appear to be inhibited substantially. Furthermore an increased lactate production associated with anaerobic glycolysis argues against a significant inhibition of lactate dehydrogenase. Thus, the role of the lactate dehydrogenase isoenzyme in the heart still needs full elucidation.

Lactate/pyruvate ratios. Clinical workers have made extensive use of the ratios between the lactate and pyruvate concentrations of blood entering and leaving the heart to calculate "excess lactate production and the redox potential across the heart.[74-76] Myocardial anoxia is held to be associated with formation of excess lactate and a negative redox potential across the heart. Some limitations of these calculations have been detailed by Olson[77] and Scheuer.[78] The use of calculations derived from the blood lactate/pyruvate ratios to indicate anaerobiosis would only be exact if (1) the heart cell membrane was freely permeable to lactate and pyruvate ions, which is not so in some systems[79, 80] and if (2) the cytoplasmic NADH/NAD ratio which regulates the cytoplasmic lactate/pyruvate ratio were closely controlled by the state of intracellular oxygenation. It should be noted that the lactate/pyruvate ratio in the tissue of the isolated rat heart is about double that in the perfusion medium.[68] The mitochondrial NADH will increase as soon as the activity of the respiratory chain is slowed by oxygen deprivation but a secondary increase in the cytoplasmic NADH depends on the activity of various hydrogen shuttles (see Section VI).[73] Glycolysis can be accelerated by a multiplicity of factors, including hormones, muscular work, and pH. Should any of these accelerate glycolysis to a degree which exceeds the capacity of the hydrogen shuttles then lactate can form from pyruvate even in the absence of anaerobiosis.[81]

Any use of lactate/pyruvate ratios must also take into account the following factors which may alter the ratio. (1) Concurrent oxidation of the FFA or ketone bodies which increases the ratio of the lactate to pyruvate found in the perfusate of the isolated rat heart[69] the change may reflect intramitochondrial generation of NADH during FFA oxidation. A high rate of ketone body utilization may explain why there is an increase in the lactate, pyruvate ratio across the heart during extracorporeal circulation.[82] Utilization of FFA is however reduced in hypoxic isolated rat hearts and in the ischemic dog heart.[83, 84] (2) The nutritional state of the animal because perfusion of hearts from diabetic or starved rats is associated with a decreased lactate pyruvate ratio[73, 85] the reason for this change is unknown. (3) Factors such as the administration of insulin and exercise which can cause pyru

vate output by the heart. Furthermore the majority of studies show that extreme degrees of arterial desaturation with coronary sinus pO₂ values of 10 mm Hg or below are required to produce significant changes in the lactate pyruvate ratio of blood leaving the heart. Even lower venous pO₂ values are required before lactate uptake by the heart changes to lactate output. These objections bring the use of lactate pyruvate ratios as sole indicators of anaerobic metabolism under suspicion. Other possible indicators such as the release of lactate or inorganic phosphate or potassium need evaluation, these may reflect cell membrane changes in hypoxia. Nevertheless, the use of lactate pyruvate values has been vindicated in the specific case of patients with ischemic heart disease by the close correlation between symptoms of angina pectoris, electrocardiographic changes, and regional production of excess lactate. It has been found that diminished myocardial lactate extraction may be a more sensitive indicator of myocardial ischemia than electrocardiographic or hemodynamic parameters. A further use of lactate pyruvate ratios is in studying patients with obstructive cardiomyopathy who have an elevation of coronary sinus lactate pyruvate ratio on exercise; this lactate pyruvate ratio may revert to normal after treatment with Pronethalol.

Rate limiting steps in anaerobic glycolysis. From the reported rates of glycogen breakdown and glucose uptake during sustained anoxia in dog and rat hearts it can be calculated that only one-tenth to one-third of the energy needs of the mammalian heart can be met by anaerobic glycolysis. This amount of energy is sufficient to maintain normal mechanical function of the dog heart during partial but not total deprivation of oxygen. Anaerobic glycolysis also helps to maintain normal activity of cellular enzyme and of the contractile system during anoxia and hastens recovery when anoxia is relieved.

However the maximal activities of phosphorylase hexokinase and phosphofructokinase are in the region of 1 to 3 mM of glucose equivalent transformed per 100 gram heart per minute (when recalculated for 37 degrees from published date). When maximally active these enzymes should be able to produce lactate anaerobically at a rate just sufficient to generate the amounts of ATP normally produced by aerobic metabolism. High rates of anaerobic glycolysis occur resulting from rapid glycogenolysis for a minute or 2 at the onset of anoxia or cyanide poisoning, and during this period anaerobic metabolism can provide a substantial part of the myocardial energy needs. In the anoxic rat heart the rate of anaerobic glycogenolysis declines long before glycogen is depleted. Thus it appears that there are factors restricting anaerobic glycolysis during anoxia. This is in contrast to the situation in the isolated perfused turtle heart in which the rates of anaerobic lactate production are such that several glycolytic enzymes appear to be working at maximal capacity. There might be practical implications in any manipulations which could be shown to increase the maximal rate of anaerobic glycolysis in the mammalian heart. For example the energy metabolism of the heart might be better sustained during angina pectoris or myocardial infarction.

One factor restricting the activity of phosphofructokinase during anoxia might be a fall in pH due to lactate accumulation. The rate of fall of pH in anoxic heart tissue is only 0.5 unit in 15 minutes, as shown by calculations based on the rate of myocardial lactate accumulation and the myocardial buffering capacity and confirmed by direct measurement. This slight fall in tissue pH is insufficient by itself to inactivate purified phosphofructokinase but the ATP-inhibited enzyme is extremely sensitive to very small changes in the physiological pH range with a low pH decreasing its affinity for fructose 6-phosphate. Conversely a high pH is associated with increased rates of glycolysis from both glycogen and glucose in the anoxic perfused turtle heart. (Since writing this section the factors controlling the rate of glycogenolysis and glycolysis in ischemic myocardium have been reviewed by Wollenberger and Krause. Glycogen the major source of glycolytic product in early anaerobic glycolysis, with the rate of conversion of phosphorylase *b* to *a* of critical

importance. This conversion is thought to be dependent on release of endogenous catecholamines by oxygen-lack. Activation of phosphofructokinase is related to the rise in Pi; subsequently, accumulation of fructose 1,6-diphosphate allows product activation. Changes in adenine nucleotide concentrations are not thought to be important in this rapid activation of glycolysis.)

Regional anaerobiosis. It has been suggested that the endocardium of the heart has a more anaerobic type of metabolism with a lower oxygen tension in the endocardium.[11] During reduced coronary flow the endocardial zone has a decreased content of CrP and increased contents of lactate and AMP.[4] However, the low oxygen tension could also be explained by postulating a greater rate of mitochondrial metabolism in the endocardium with a higher qO_2, while a greater reliance on respiration of FFA could explain increased lactate and lactate/pyruvate ratios. More knowledge of the distribution of the enzymes of glycolysis, of fatty acid oxidation and of mitochondrial metabolism is required before these possibilities can be fully evaluated. Nevertheless, relative anaerobiosis of the subendocardium is an attractive hypothesis to explain the occurrence of ischemia, infarction, and fibrotic processes in the endocardial zone of the human heart. (Since writing this section, measurements of glycolytic enzymes in the inner and outer myocardium have been reported;[11] the results support the concept of relative subendocardial ischemia.)

Glycolysis in heart failure. Increased glycolysis may occur in various experimental types of heart failure.[113, 11] Furthermore, there is an increase of glycolytic enzymes relative to those of the citrate cycle in human heart failure.[117] These data are consistent with an increased anaerobic metabolism in heart failure. On the other hand, the oxygen uptake of the human heart and of the isolated heart[118] is normal in failure, which suggests that anaerobic metabolism does not play any significant role in energy production in the failing heart, except in acute or terminal situations.

Therapeutic use of glucose. The use of the KCl-glucose-insulin regime in the therapy of myocardial infarction is referred to later. Although intravenous glucose solutions have been used in attempts to improve the contractility of the failing human heart, there are no well-documented studies. Hypertonic glucose or lactate solutions can increase stroke volume and heart work of anesthetized dogs; these effects are presumably, at least in part, related to changes in the circulating blood volume.[119, 120] Glucose appears to be required for optimal contractility of the isolated rat atrium, stimulated diaphragm, and the substrate-depleted isolated rat heart.[121, 122] The explanation of these results is at present unknown, but they do suggest that clinical trials to assess the value of glucose therapy in patients with failing hearts might be warranted.

Glucose metabolism: conclusions. (1) Membrane transport is of major importance in controlling the rate of glucose uptake by the isolated rat heart. This process is stimulated by insulin, anoxia, and muscular work, which also increase the rate of glycolysis by increasing the activity of phosphofructokinase. (2) The use of calculations derived from the lactate/pyruvate ratio of blood entering and leaving the heart as sole indicators of anaerobic metabolism is criticized both on theoretical grounds and because of the severe degree of hypoxia required to produce excess lactate. However, the practical value of measurements of lactate/pyruvate ratios has been proved in ischemic heart disease and in the assessment of obstructive cardiomyopathy. (3) From the in vitro activities of phosphorylase, hexokinase, and phosphofructokinase, and from the maximal reported rates of anaerobic glycolysis, it can be anticipated that anaerobic glycogenolysis and glycolysis should be able to contribute significantly to energy production in the working mammalian heart. However, the failure of these anaerobic processes to maintain the anoxic heart may indicate the presence of restraints on anaerobic energy production.

II. Glycogen metabolism

Glycogen synthesis. Glucose is the only effective exogenous glycogen precursor in the heart because of the absence of the enzyme fructose 1,6-diphosphatase.[33, 123] In

the isolated perfused rat heart both incorporation of carbon from glucose into glycogen and net glycogen synthesis are greater in fed than in fasted states, and the glycogenic effect of insulin is lost in the fasted state.[illegible] Also an increased circulating glucose concentration (as found in the postprandial state) promotes glycogen synthesis.[illegible] Thus, in the fed state there is increased glycogen synthesis which occurs especially in the outer chains.[illegible] Nevertheless the glycogen content of the fed heart is 2 to 3 times lower than that found in the fasted state.[illegible] The inference is that glycogen degradation and turnover are higher in the fed state. Conversely in the fasted and diabetic states the higher glycogen may be looked upon as a reflection of decreased glycolysis and sparing of glycogen associated with increased FFA or ketone metabolism by the heart.[illegible] Such elevation of cardiac glycogen depends in part on a pituitary factor probably growth hormone which is thought to act by FFA mobilization and consequent sparing of glycogen.[illegible] There is also decreased glycogen turnover in the fasted heart as shown by a lower rate of incorporation of ^{14}C-glucose into glycogen and decreased glycogenolysis during exercise.[illegible]

Glycogen synthesis occurs by transfer of the glucose moiety of uridine diphosphate glucose to an acceptor polyglucose chain under the influence of glycogen synthetase.[illegible] Glucose moieties are first added to peripheral glycogen chains and then transferred inward.[illegible]

Glycogen synthetase exists in 2 forms the I (independent) form which is active in the absence of the glycogen precursor G-6-P whereas the D form requires the presence of G-6-P for its activity. In the isolated perfused working rat heart over 90 per cent of the synthetase is in the D form.[illegible] The half maximal concentration of G-6-P required to activate skeletal muscle glycogen synthetase is in the neighborhood of 600 μM,[illegible] a level which can be reached in both skeletal muscle in vivo[illegible] and in the rat heart in vivo.[137] ATP is required to keep glycogen synthetase in the D form because I to D conversion requires phosphorylation of the enzyme protein by ATP Mg^{++} in the presence of cyclic AMP this phosphorylation is catalysed by synthetase I kinase.[illegible] Thus during severe ATP-depletion there is a rapid conversion of D to I synthetase.[illegible] Such a degree of ATP-depletion is unlikely to occur physiologically. Another mechanism converting the D to the I form is hormonal after an insulin injection to the rat in vivo total synthetase activity is unchanged but about 75 per cent is now in the I form.[illegible] Various conflicting effects are reported for catecholamine stimulation (see later). The suggestion that increased tissue glycogen stores inhibit glycogen synthesis by decreasing the percentage of I synthetase[illegible] has been confirmed in the cat heart in situ[illegible] but not in the perfused working rat heart.[illegible]

At present knowledge of the control of heart glycogen synthetase is inadequate to explain why glycogen synthesis is decreased in diabetes mellitus, a condition known to be associated with high G-6-P levels in the heart.[illegible] The possibility of an alternate pathway of glycogen synthesis not involving G-6-P as an intermediate cannot be excluded.[illegible]

Glycogen degradation. Although the ensuing discussion is limited to the function of phosphorylase in glycogen breakdown debranching enzymes such as α-glucosidase (maltase) are also essential for glycogenolysis and their absence can produce the fatal disease known as cardiomegalic glycogenosis or Pompe's disease.[illegible]

Phosphorylation distribution in the myocardium approximates to that of glycogen and increases from epicardium to endocardium.[illegible] Ventricular tissue contains more phosphorylase activity than atrial tissue.[illegible] Phosphorylase b can undergo dimerization and phosphorylation to yield the active *a* form under the catalysis of phosphorylase *b* kinase. This kinase is in turn activated by cyclic AMP.[illegible] In the working rat heart catecholamines activate phosphorylase within seconds of an increase in the concentration of cyclic AMP.[illegible] The cyclic AMP is formed from ATP via the adenyl-cyclase system[illegible] which is found in particulate preparations from the dog heart.[illegible] Once formed cyclic AMP can be hydrolysed by a phosphodiesterase normally present in the muscle.[illegible] Increased conversion of phosphorylase *b* to *a* is important

in the immediate response to myocardial ischemia following coronary artery ligation in the dog rabbit, or rat this conversion is probably mediated by release of endogenous catecholamines from the heart by ischemia.[148] Other factors influencing cardiac phosphorylase activity include (1) the thyroid hormones which in the rat in vivo increase the percentage of phosphorylase in the *a* form by potentiation of the response of the phosphorylase system to catecholamines[149] (2) glucagon which also increases the percentage of phosphorylase *a*[83,144] and (3) possibly muscular contraction Contraction activates skeletal muscle phosphorylase *b* kinase by a mechanism which is independent of cyclic AMP and may involve Ca^{++} and a protein cofactor[150] A similar activating mechanism may exist in the heart because Ca^{++} and a kinase activating protein can activate purified phosphorylase *b* kinase from the beef heart.[134] However catecholamines appear to be the most important of the known stimuli which convert phosphorylase *b* to *a*.

Phosphorylase *b* is also activated directly by AMP and thus may be especially important in sustained anoxia in the isolated heart.[131,138] Phosphorylase *b* is inhibited in vitro by ATP ADP and G-6-P at concentrations which may be present intracellularly During anoxia, the following factors contribute to enhanced glycogenolysis decreased ATP increased Pi, and the decreased G-6-P which follows an enhanced rate of glycolysis.[131,138] Increased AMP levels increase the affinity of phosphorylase *b* for its substrates, glycogen and Pi. The similarity of the changes in adenine nucleotides (during anoxia and muscular work) that stimulate phosphorylase and phosphofructokinase, strongly suggests integrated control mechanism for both enzyme activities.[71,131,138]

Relation between hormonal and cellular control of glycogen metabolism Newsholme[139] has discussed the advantages of dual mechanisms, hormonal and cellular in the control of glycogen metabolism In the case of both synthetase and phosphorylase of skeletal muscle glycogen hormonal control converts the enzyme from a form partly controlled by a cellular metabolite to an insensitive form Catecholamines also stimulate phosphorylase *b* to *a* conversion in the heart, thereby allowing the phosphorylase to escape from the ATP and G-6-P inhibition prevailing in the aerobic cell[134] while insulin makes the rat heart muscle glycogen synthetase much less sensitive to the intracellular concentration of G-6-P[139] Thus hormonal regulation bypasses a cellular control mechanism It is postulated that the large number of intermediate steps between stimulation of the adenylcyclase system by catecholamines and activation of phosphorylase may serve as an amplification system.[139]

In the heart tissue however there is no concrete evidence to support the role of catecholamines in the control of glycogen synthetase. In the isolated heart, catecholamines are variously reported to stimulate synthetase I activity[156] or not to alter activity[80] In the rat heart in situ, synthetase I activity increases after an intravenous injection of epinephrine or in the initial minutes of an epinephrine infusion, while a simultaneous increase of phosphorylase activity explains why total cardiac glycogen is unaltered[155,156,158] These complex findings may be related to the following interrelations (1) the relative degrees of stimulation of the phosphorylase and glycogen synthetase systems, which are simultaneously stimulated in contrast to findings in skeletal muscle in which glycogen phosphorylation activation is accompanied by inactivation of glycogen synthetase[151,156,157] (2) the degree of accumulation of G-6-P as a result of the effects of catecholamines and muscular work on glucose uptake and phosphofructokinase activity because G-6-P inhibits phosphorylase and activates glycogen synthetase D (3) the degree of accumulation of cyclic AMP which stimulates the kinase which activates glycogen synthetase I[158] and (4) the ability of catecholamines to mobilize FFA in the intact animal with increased myocardial FFA uptake and consequent sparing of glycogen.[13,14] It should be emphasized that studies with catecholamines are difficult to interpret because of the marked influence of the dosage used and the manifold effects on coronary blood flow cardiac contractility FFA usage, and the systems synthesizing and degrading glycogen.

the isolated perfused rat heart both incorporation of carbon from glucose into glycogen and net glycogen synthesis are greater in fed than in fasted states and the glycogenic effect of insulin is lost in the fasted state.[15] Also an increased circulating glucose concentration (as found in the postprandial state) promotes glycogen synthesis.[11] Thus in the fed state there is increased glycogen synthesis, which occurs especially in the outer chains.[128] Nevertheless, the glycogen content of the fed heart is 2 to 3 times lower than that found in the fasted state.[134] The inference is that glycogen degradation and turnover are higher in the fed state. Conversely, in the fasted and diabetic states the higher glycogen may be looked upon as a reflection of decreased glycolysis and sparing of glycogen associated with increased FFA or ketone metabolism by the heart.[11, 43,127,133] Such elevation of cardiac glycogen depends in part on a pituitary factor probably growth hormone which is thought to act by FFA mobilization and consequent sparing of glycogen.[129,131] There is also decreased glycogen turnover in the fasted heart as shown by a lower rate of incorporation of ^{14}C-glucose into glycogen and decreased glycogenolysis during exercise.[83,130,132]

Glycogen synthesis occurs by transfer of the glucose moiety of uridine diphosphate glucose to an acceptor polyglucose chain under the influence of glycogen synthetase.[135] Glucose moieties are first added to peripheral glycogen chains and then transferred inward.[134]

Glycogen synthetase exists in 2 forms the I (independent) form which is active in the absence of the glycogen precursor G-6-P whereas the D form requires the presence of G-6-P for its activity. In the isolated perfused working rat heart over 90 per cent of the synthetase is in the D form.[136] The half maximal concentration of G-6-P required to activate skeletal muscle glycogen synthetase is in the neighborhood of 600 μM [138] a level which can be reached in both skeletal muscle in vivo[136] and in the rat heart in vivo.[137] ATP is required to keep glycogen synthetase in the D form because I to D conversion requires phosphorylation of the enzyme protein by ATP Mg^{++} in the presence of cyclic AMP thus phosphorylation is catalysed by synthetase I kinase.[139] Thus, during severe ATP-depletion there is a rapid conversion of D to I synthetase.[138] Such a degree of ATP-depletion is unlikely to occur physiologically. Another mechanism converting the D to the I form is hormonal after an insulin injection to the rat in vivo total synthetase activity is unchanged but about 75 per cent is now in the I form.[140] Various conflicting effects are reported for catecholamine stimulation (see later). The suggestion that increased tissue glycogen stores inhibit glycogen synthesis by decreasing the percentage of I synthetase[138] has been confirmed in the cat heart in situ[407] but not in the perfused working rat heart.[136]

At present knowledge of the control of heart glycogen synthetase is inadequate to explain why glycogen synthesis is decreased in diabetes mellitus, a condition known to be associated with high G-6-P levels in the heart.[27,137] The possibility of an alternate pathway of glycogen synthesis not involving G-6-P as an intermediate cannot be excluded.[140]

Glycogen degradation. Although the ensuing discussion is limited to the function of phosphorylase in glycogen breakdown debranching enzymes such as α-glucosidase (maltase) are also essential for glycogenolysis and their absence can produce the fatal disease known as *cardiomegalic glycogenosis* or Pompe's disease.[144a]

Phosphorylation distribution in the myocardium approximates to that of glycogen and increases from epicardium to endocardium.[142] Ventricular tissue contains more phosphorylase activity than atrial tissue.[142] Phosphorylase *b* can undergo dimerization and phosphorylation to yield the active *a* form under the catalysis of phosphorylase *b* kinase. This kinase is in turn activated by cyclic AMP.[143] In the working rat heart, catecholamines activate phosphorylase within seconds of an increase in the concentration of cyclic AMP.[144] The cyclic AMP is formed from ATP via the adenyl cyclase system,[88] which is found in particulate preparations from the dog heart.[145] Once formed cyclic AMP can be hydrolysed by a phosphodiesterase normally present in the muscle.[77] Increased conversion of phosphorylase *b* to *a* is important

sufficient first class binding sites of strongest affinity for FFA available for the association of 1.2 mM of FFA (data calculated from Goodman[79]) which is an FFA concentration rarely exceeded in vivo even in fasting or in diabetic patients.[100,101] There are no known direct hormonal influences on FFA uptake by the heart in particular the process is not insulin sensitive in the dog in vivo.[88]

The molecular structure of the fatty acid chain may regulate FFA uptake when the isolated rat heart is perfused with equimolar mixtures of fatty acids.[82] Monounsaturated acids (e.g. oleate) are taken up and oxidized more readily than the corresponding saturated (e.g. stearate) or diunsaturated (e.g. linoleate) acids, while uptake of saturated acids decreases as the chain length increases.[82] [4] The situation in the human heart is more complex because the circulating concentration of each fatty acid varies, but it appears that approximately similar principles apply.[71,100-114] These differences in the uptake of FFA by the heart may be in part explained by the molecular structure of the FFA which influence the affinity of binding by carrier albumin and the rate of disposal of intracellular FFA by oxidation.[82,17,114] There is no apparent explanation for a contradictory finding that the isolated rat heart extracts fatty acids of various chain lengths indiscriminately.[88]

Intracellular fate of FFA. Intracellular FFA has been detected in the heart in situ and in the perfused rat heart. It can be derived from the uptake of FFA or triglycerides from the circulation[83,114] or from the breakdown of endogenous glycerides (chiefly triglyceride).[83] The values measured in the rat heart in vivo vary from 10 to 20 μM per gram wet weight[117] [87] to about 0.5 μM per gram.[88] If the higher values (some measured on instantly frozen hearts) are correct then the heart FFA level is about 20 times that of the blood. In the perfused rat heart the intracellular content of tetramethylmyristate a non-oxidizable fatty acid analogue is also higher than in the perfusing fluid.[88] These data are consistent with the presence of intracellular binding sites with high affinity for FFA. It is not necessary to postulate the existence of a concentrating mechanism. There is, in fact, some evidence that intracellular FFA is bound to an intracellular protein site.[89] After activation intracellular FFA can be oxidized or form tissue lipids, and the following lines of evidence suggest that the removal of intracellular FFA by oxidation can influence the uptake of FFA by the isolated rat heart (1) the correlation between rates of uptake and oxidation of FFA[82] (2) the accumulation of intracellular FFA when fatty acid oxidation is blocked by the addition of acetoacetate[88] or by an alteration in the structure of the chain[88] and (3) the accumulation of intracellular FFA when the oxidative capacity of the system is exceeded by high circulating FFA concentrations.[116] The release of FFA from the heart into the perfusing medium when the circulating concentration is low[17] suggests that intracellular and extracellular FFA can be in a two-way equilibrium. This is not, however a simple equilibrium because of the pattern of fatty acids in intracellular and extracellular FFA differ in vivo.[84]

Endogenous lipid as fuel for contraction. Release of oxidizable fatty acids during hydrolysis of endogenous lipids occurs when the isolated rat heart is perfused with a substrate-free medium.[81] [83] An earlier suggestion that phospholipid is used in such conditions[87] has not been confirmed and it is the triglyceride fraction that is used.[84,118] In the absence of FFA or glucose plus insulin in the perfusate, hydrolysis of triglyceride can account for the major part of the heart's oxygen uptake probably even during the enhanced glucose uptake associated with increased work of the isolated rat heart. However not all triglyceride is available for such purposes because about one fifth or more of triglyceride remains in the isolated heart even when exhausted by substrate depletion.[88] [84] The constancy of the phospholipid fraction suggests that it is chiefly a structural lipid. There is no evidence to suggest that endogenous lipid is an energy source for the normal heart *in situ* except during intense exercise[117] or prolonged fasting.[83]

Carnitine. Carnitine (β-hydroxy-γ-trimethyl ammonium butyrate) is a normal constituent of many tissues, but the levels

in the heart are especially high.[illegible] Carnitine catalytically increases the oxidation of long chain fatty acids by heart homogenates and mitochondria.[illegible] When heart mitochondria are incubated with carnitine and palmitate, palmitylcarnitine is formed simultaneously with the stimulation of oxidation.[illegible] The cofactor requirements for this reaction correspond exactly to those of fatty acid activation,[illegible] which suggests that fatty acyl CoA is first formed by acyl CoA synthetase:

$$\text{Palmitate} + \text{CoA} + \text{ATP} \xrightarrow{Mg^{++}} \text{palmityl CoA} + \text{AMP} + \text{PP}$$

Acyl CoA undergoes reversible transacylation with carnitine[illegible]:

$$\text{Palmityl CoA} + \text{carnitine} \rightleftharpoons \text{palmitylcarnitine} + \text{CoA}$$

The enzyme concerned, carnitine acyltransferase, is found in both mitochondria and the 25,000 g supernatant of rat heart preparations.[illegible] In liver mitochondria the activity of this enzyme is thought to be rate limiting for both palmitate and palmityl CoA oxidation.[illegible]

The carnitine system may help to regulate the rate of FFA oxidation by tissues. In the absence of carnitine, transport of acyl CoA to the fatty acid oxidase system becomes limiting,[illegible] and the presence of carnitine is virtually obligatory for oxidation of long-chain FFA by heart mitochondria.[illegible]

The existence of the carnitine system may also explain the decrease in FFA oxidation by the isolated rat heart in the presence of high concentrations of pyruvate or glucose.[illegible] The addition of pyruvate to equimolar acetylcarnitine decreases the rate of utilization of acetylcarnitine by kidney mitochondria, and in general heart and kidney mitochondria have similar carnitine systems.[illegible] Bremer[illegible] reported a preliminary experiment in which pyruvate spared the mitochondrial utilization of octanylcarnitine. He suggested that there was competition for available mitochondrial CoA.

Triglyceride accumulation in pathological states. Cardiac triglyceride is increased in the following experimental states: diphtheritic myocarditis, alloxan-diabetes, alcohol-infusion, norepinephrine-infusion and myocardial hypoxia. Lipid accumulation in the heart also occurs in the clinical counterparts of these conditions, which are respectively human diphtheritic myocarditis, alcoholic cardiomyopathy, catecholamine induced cardiac necrosis, and myocardial infarction (and possibly the "tabby-cat" heart of severe anemia).

In *diphtheritic myocarditis* triglyceride accumulation is associated with a depressed rate of oxidation of FFA and a decreased content of carnitine.[illegible] The rate of palmitylcarnitine synthesis is decreased and it is inferred that there is interference with the transfer of long-chain fatty acids into the mitochondria.[illegible] These findings support the suggestion of Fritz[illegible] that the availability of carnitine may determine whether acyl CoA is oxidized or forms triglyceride.

In hearts from rats with *alloxan-diabetes* there is an increased triglyceride content[illegible] associated with the formation of numerous lipid droplets visible by light microscopy.[illegible] In isolated rat hearts from diabetic rats perfused with glucose and insulin there are associated increases in both the rates of glyceride glycerol synthesis from glucose and in the rates of glyceride hydrolysis; the increased hydrolysis contributes fatty acid for the energy metabolism of the perfused heart.[illegible] Thus there is a triglyceride cycle, which undergoes increased turnover in alloxan-diabetic hearts. In such hearts the availability of L-glycerol 3-phosphate does not appear to help regulate the rate of glyceride synthesis.[illegible] The myocardial content of glycerol phosphate is actually decreased in spite of an increased flow of glucose carbon to glyceride-glycerol. In starvation, too, the myocardial glycerol phosphate content is decreased even though the myocardial glyceride is increased.[illegible] The increased myocardial glyceride of alloxan-diabetes and starvation depend on the availability of hormones (growth hormone and corticosteroids) which mobilize FFA from adipose tissue. Therefore in these conditions increased heart glycerides are thought to be related to increased myocardial uptake of circulating FFA.[illegible]

During a *norepinephrine infusion* into the dog, there are increased lipid droplets in the heart, in association with FFA

mobilization.[184] When, however, norepinephrine is infused directly into the coronary arteries of dogs, triglyceride accumulation can be related to increased uptake of circulating blood triglyceride fatty acid.[31] The relationship of triglyceride accumulation to catecholamine-induced myocardial necrosis has not been clarified.[31] It may be pertinent that another condition associated with triglyceride accumulation, *alcoholic heart disease*, also results in myocardial fibrosis, and histochemical changes similar to those observed in catecholamine-induced necrosis.[201] Alcoholic heart disease is further discussed in Section X.

Myocardial hypoxia is associated lipid accumulation[34] in the form of triglyceride.[33, 34] In the ischemic dog heart, triglyceride accumulation has been thought to be related to increased availability of L-glycerol 3-phosphate derived from anaerobic glycolysis.[34] While it is reasonable to expect an increased glycerol phosphate in the ischemic heart (because of increased cytoplasmic reduced pyridine nucleotide), there is the previously detailed evidence that glycerol phosphate availability does not *usually* help to regulate the rate of glyceride synthesis in the heart.

Glycerol phosphate in the heart is *not* derived solely from glycolysis, because both the isolated rat heart and the human heart can take up circulating glycerol,[203, 205] and in the rat there is sufficient glycerolkinase activity to form glycerol phosphate at a rate comparable to that formed during the uptake of glucose by the isolated heart.[205A] The failure of Scheuer and Olson[32] to detect glycerol uptake by the isolated rat heart could be explained by postulating a decreased glycerolkinase activity in fasted rats, which they used.

Myocardial triglyceride frequently appears to increase in conditions in which FFA can accumulate intracellularly, as when FFA uptake is enhanced by alloxan-diabetes[36] or by a catecholamine infusion.[193] In the anoxic isolated rat heart, increased triglyceride formation from [14]C palmitate can be related to increased intracellular [14]C FFA associated with decreased FFA oxidation by the heart.[33] Similarly, when FFA oxidation is blocked by pyruvate or acetoacetate there is increased incorporation of FFA carbon into intracellular FFA and glycerides concomitantly with a reduced rate of FFA oxidation.[199]

Intracellular FFA can also be derived from exogenous triglyceride fatty acid from lipoproteins[214] or chylomicrons.[194] Thus increased intracellular FFA could also explain myocardial triglyceride accumulation during the enhanced uptake of circulating triglycerides,[31, 32] as occurs when dogs are infused with ethanol or catecholamine. There is as yet no indication of the mechanism whereby the level of intracellular FFA could help to regulate myocardial triglyceride metabolism.

Uptake and fate of ketone bodies. Acetoacetate and β-hydroxybutyrate are taken up and oxidized by the isolated rat heart[41, 23] and by the dog and human heart in situ.[21, 218] In the isolated rat heart, the importance of acetoacetate as substrate is determined by the circulating concentrations: the utilization of acetoacetate, 5 mM, can account for 73 to 82 per cent of the total oxygen uptake, while 0.25 mM acetoacetate (a concentration higher than that in the blood of well fed rats) accounts for 36 per cent of the myocardial respiration. When acetoacetate is infused into the intact dog, this substrate can account for the major part of respiration only when the circulating concentration is between 3 and 6 mM; at higher concentrations the myocardial extraction abruptly ceases for obscure reasons.[21]

β-hydroxybutyrate is the major ketone body taken up by the human heart and its arterial concentration exceeds that of acetoacetate by 3 to 8 times.[13, 21] The appropriate enzymes for the oxidation of β-hydroxybutyrate have been found in the rat or pig heart.[219, 220] When acetoacetate is the major substrate of the isolated rat heart or the intact dog heart, the major fates are oxidation or reduction to β-hydroxybutyrate; the rate of reduction of acetoacetate is influenced by the availability of mitochondrial NADH$_2$, and hence both by the state of tissue oxygenation and by the rate of reduction of NAD by other substrates.[41, 220, 221] β-hydroxybutyrate and acetoacetate may act as a couple whose ratio reflects the intramitochondrial free NADH$_2$/NAD ratio[222] in the isolated

heart this ratio appears to be 0.1.[illegible] This relationship between the mitochondrial NADH and the β-hydroxybutyrate:acetoacetate couple explains why the β-hydroxybutyrate:acetoacetate ratio rises across the human heart and why acetoacetate is more readily extracted (in relation to its arterial concentration) than β-hydroxybutyrate.[illegible]

There is no evidence that ketone bodies are ever a major substrate of the normal human heart. In the postabsorptive state after an overnight fast when the circulating ketone concentration is about 0.1 to 0.3 mM/L,[illegible] the uptake of ketones can account for only 5 to 9 per cent of the total myocardial oxygen uptake during rest and for even less during exercise.[illegible] Even in fasting adult diabetic patients deprived of insulin for 24 hours or more ketones can account for only 10 per cent of the total oxidative metabolism of the heart.[illegible] It is however anticipated that ketones may contribute significantly to the energy metabolism of the heart in severe diabetic ketosis.

The discrepancy between the rates of ketone body uptake by the hearts of experimental animals and of humans may be due to the higher concentrations of ketones (as the sole substrate) usually presented to the heart in animal experiments or to a species difference. It does however appear to be incorrect to generalize from experiments on the isolated heart and to conclude that ketone bodies are the preferred substrate for the heart[illegible] except in extreme conditions such as starvation or severe ketosis.

FFA and ketone metabolism: conclusions. (1) The uptake of FFA by the heart has been studied extensively in vivo and in vitro. FFA uptake depends on the concentration of circulating FFA and the molecular structure of the fatty acid. In vivo and in vitro there appears to be a threshold level below which FFA uptake does not occur. The FFA:albumin molar ratio appears only to influence the rate of FFA uptake when the albumin concentration is lower than levels usually found in vivo. (2) In vitro the rate of FFA oxidation is determined by the rate of FFA uptake, the presence and concentration of competing substrates, and the operation of the carnitine system. (3) Triglyceride accumulates in the heart in diphtheritic myocarditis, alloxan-diabetes, during infusions of alcohol and norepinephrine and during myocardial hypoxia. In the majority of cases, there is a concomitant reduction of FFA oxidation by the heart and it is suggested that accumulation of intracellular FFA may lead to increased triglyceride levels. (4) Ketone bodies, although an important energy source when presented to the isolated rat heart as the only substrate, are not important for the energy metabolism of the normal human heart.

Fundamentals of clinical cardiology

Physiological considerations in cerebrovascular disease

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Cerebrovascular disease accounts for about 14 per cent of the over-all mortality figures and it is also responsible for much chronic morbidity. Examination of the physiological and hemodynamic factors involved has led to a greater understanding of this problem in recent years.

Anatomy

The anatomical arrangement of the cerebral vessels needs no comment except to emphasize some points of functional importance. The external and internal carotid systems are quite separate physiologically, though they may communicate significantly in certain circumstances. Anastomoses between the major arteries within the cranium may occur at two principal levels. The circle of Willis is a built-in and usually functional anastomosis, though subject to considerable variation, which is capable of effecting uniform distribution of vascular inputs into the cranium before final delivery to the brain itself. There are also extensive potential anastomoses between pial vessels at cortical level, though after penetration the vessels are in effect end arteries. The largest amount of blood to the brain is supplied centripetally, as would be expected from the late phylogenetic development of the cerebral hemispheres, but a centrifugal supply arising directly from the circle of Willis or the proximal few centimeters of the main cerebral arteries, is responsible for some of the deep gray masses and the ventral part of the brain stem. This arrangement gives rise to "watershed" areas in two planes: between the terminal branches of the main cerebral vessels both on the surface of the hemisphere and deep to this, and also between the centripetal and centrifugal supplies—usually deep in the white matter and in the periventricular regions. These considerations may be important in determining the site of lesions in conditions affecting the whole vascular tree, such as changes in perfusion pressure (hypertension or hypotension), alterations in blood viscosity, and severe anoxia.

Physiology

The extracranial vessels behave in the same way as peripheral vessels throughout the body; that is, the vessel tone is determined by the autonomic nervous system and the flow of blood is pressure dependent. The internal carotid system is physiologically quite distinct; sympathetic stimulation has virtually no effect and flow is independent of perfusion pressure over a very wide range. The brain, with a respiratory quotient of unity, derives its energy solely from glucose and oxygen, since

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neither of these is stored and the turnover is relatively high, ischemia produces an effect almost immediately and irrecoverable damage in a few minutes—damage which cannot be rectified by any subsequent healing process.

Maintenance of the cerebral circulation is therefore essential and must take precedence over fluctuating demands elsewhere. This is ensured to some extent by the baroreceptors and chemoreceptors in the aortic arch, carotid arteries, and carotid body. These receptors supply information to the central regulatory mechanisms which control the systemic pressure and the rate and depth of respiration.

The physiology of the cerebral circulation can be conveniently considered by discussion of the variable factors involved; this subject has been reviewed by Lassen. As with any hemodynamic system, the flow is proportional to the perfusion pressure and inversely to the vascular resistance. The perfusion pressure across an organ is the mean arterial blood pressure (MABP) minus the venous pressure. For practical purposes the latter is usually ignored. This is reasonable since the jugular venous pressure approximates to zero in comparison to the systemic pressure and there is not much fluctuation. It does, however, become of considerable importance under high gravitational stress when the cerebral circulation may be maintained in spite of an inadequate systemic pressure by a siphoning effect due to an even lower pressure in the jugular system, and under these conditions gray matter flow is preserved at the expense of white matter flow.

Cerebral blood flow is maintained at a constant rate over a wide range of systemic pressure, about 70 to 150+ mm. Hg MABP, provided that the pCO_2 remains within the normal range. This is achieved by constriction of arterioles in face of a rising head of pressure (Bayliss' effect), thus increasing the cerebrovascular resistance. This is a myogenic response not mediated by chemical stimuli or neuronal pathways and independent of the cause of the hypertension. It may be the natural response of smooth muscle to potential stretch when its response is not modified by sympathetic activity, since a sympathectomized external carotid system behaves in a similar way. Below about 70 mm. Hg MABP compensation ceases and flow becomes pressure dependent. At high pressures spasm may occur, but the clinical outcome depends more on the state of the vessels.

The cerebrovascular resistance is compounded of many variables. These fall into two groups—changes in the physical and chemical properties of the blood and changes affecting the vessel wall. There is great interest at present in the factors which influence the rheological properties of blood. This is an extremely complex subject because of the many factors involved and because blood does not behave as a pure Newtonian fluid owing to the presence of suspended red cells. Any variation in the number of cells in a given volume of blood has a disproportionate effect on flow, especially in the very small vessels when the size of the cells approximates to the size of the tube. Furthermore, as with all fluids, there is a critical flow rate below which laminar flow ceases and resistance rises sharply. Other factors such as platelet stickiness, tendency to red cell agglutination, and changes in the constituents of plasma may also be important. As would be expected, therefore, increased cell mass produces a profound fall in cerebral blood flow and in polycythemia rubra vera, where there is also a thrombotic tendency, obstruction of small vessels in the brain is very common. High flow rates are found in anemia, but this is probably due to an anoxic stimulus rather than any change in viscosity, since the flow rate rises according to the severity of the anemia, but the changes in viscosity are relatively small.

The most important single factor in the regulation of cerebrovascular resistance is the pCO_2, which is usually considered to act directly on the vessel, but recent evidence suggests that the effect may be mediated by brain-stem centers.[16,17] There is approximately a 2.5 per cent change in cerebral blood flow for every 1 mm. Hg change in pCO_2. This is a sensitive autoregulatory mechanism which ensures that the blood supply is adjusted to the metabolic demands. A fall in pO_2 will also cause a rise in blood flow due to anoxia, but an increase in

pO_2 has little effect. These are acute responses so that subjects living at high altitudes regain normal flow rates after a period of acclimatization.

Factors affecting the blood vessels independent of the circulating blood include the intracranial pressure and degenerative disease. Raised intracranial pressure has very little effect on cerebral blood flow probably because of a number of compensatory mechanisms, until it reaches about 400 mm H_2O.

Degenerative disease may have a profound effect on cerebral blood flow either as a result of obstruction of the major vessels in the neck or because of diffuse small vessel disease. It is of considerable interest that degenerative disease sufficient to impair cellular perfusion to a considerable extent does not impair the vessel's ability to increase blood flow when stimulated with CO_2. The ability of the cerebral vessels to alter the cerebrovascular resistance by change in vascular diameter is a response which can be evoked by several different stimuli including pressure changes, anoxia, and carbon dioxide: the first of these is probably mechanical and the others chemical. Harper[4] and Haggendal and Johansson[7] have shown that if the autoregulatory capacity is already fully committed by one factor, e.g., by a change in pCO_2, flow passively follows changes in perfusion pressure.

Development of collateral circulation. A variety of compensatory mechanisms are available if obstruction of a vessel occurs, depending on the site. There are three principal levels of collateral supply: between the external and internal carotid artery or vertebral artery in cases of lower internal carotid artery obstruction, around the circle of Willis for obstruction anywhere in the carotid or vertebral systems, and at cortical level for obstruction of a major vessel at or just distal to the circle of Willis.

In the first example blood may reach the carotid siphon by retrograde flow down the ophthalmic artery from terminal branches of the facial, maxillary, and superficial temporal arteries. Anastomoses may develop between the occipital artery and meningeal branches of the vertebral artery in patients with lower vertebral artery obstruction. Autoregulation still occurs when the main supply to the intracranial vessels is from the external carotid via these collateral channels.

The circle of Willis is an anastomotic system fed from below by the two internal carotid arteries and the basilar artery. Theoretically there should be three nodal points in the circle of Willis where the pressures in the carotid arteries and basilar artery balance and where there should be no flow. These points are in the anterior communicating artery (balance between the pressures in the two carotid arteries) and in both posterior communicating arteries (balance between the pressures in the carotid artery and the vertebral artery). This state probably never occurs in vivo partly because of the wide variation in the morphology of the circle and partly because pressures in the major vessels vary from time to time. Compensation for an obstruction below the circle can be very effective so that if one carotid is occluded a pressure sufficient to ensure near normal flow can develop in its territory and there may be no symptoms or clinically detectable neurological deficit.

Obstruction of a major vessel at or just distal to the circle of Willis stimulates the development of anastomotic channels with the terminal cortical branches of the other major vessels. If the middle cerebral artery becomes occluded, the callosomarginal and pericallosal arteries supply the upper middle cerebral artery territory (frontal and parietal lobes) and the posterior cerebral artery supplies the inferior part (temporal lobe).

The development of an efficient collateral circulation depends on the rate of development of obstruction and on the state of the remaining vessels. Meyer and Denny-Brown have shown that the most important factor influencing the collateral circulation in the pial vessels of the monkey following proximal occlusion of a major vessel is a reduction in the local head of pressure with immediate dilatation and the establishment of a pressure gradient which enables filling to occur from neighboring vessels.

Established stroke. Established strokes are usually due to hemorrhage, thrombosis, or emboli. It may be impossible to determine which of these is responsible, but a

number of features weigh the balance of probability. Emboli are likely if there is an obvious or suspected source of emboli either from the heart or from the neck vessels in which case there may be a bruit. The presence of a bruit must mean that there is turbulence but does not necessarily signify a pathological condition. Single large emboli cause strokes of sudden onset with maximal neurological deficit at the time of occurrence; there is often no evidence of pre-existing cerebrovascular disease and consciousness is not usually impaired.

Thrombosis and hemorrhage may be clinically indistinguishable. It is often said that hemorrhage is of sudden onset, frequently associated with impaired consciousness, hypertension, and a bad prognosis whereas thrombosis gives rise to a gradual increase in neurological signs over a period of hours, often occurs at night and is associated with a relatively good prognosis. Neither of these descriptions are altogether true and these points cannot be relied upon. The finding of a heavily bloodstained cerebrospinal fluid (CSF) is strongly indicative of a hemorrhage but some blood may be found following thrombosis and the absence of blood is no guide since a hemorrhage may remain intracerebral. A fourth type of the completed stroke is due to an area of cerebral infarction not obviously caused by an embolus or thrombosis and is usually associated with atheroma in the neck vessels. It is important to remember that cerebral tumors, aneurysms, and angiomata may give rise to the clinical picture of a completed stroke. A number of these patients will therefore require further investigation.

Over the years a number of special treatments have been used with the hope of minimizing the eventual disability. Stellate ganglion block was employed because it was thought that this might increase the blood flow to an ischemic area; it is now known that this has no effect. Inhalation of CO_2 (5 per cent) has been used for the same reason; its efficiency as a cerebral vasodilator is beyond question, but there are theoretical grounds for thinking that it may do more harm than good. The blood vessels near an ischemic area are fully dilated so that CO_2 inhalation would only cause vasodilation elsewhere and this might give rise to an "intracranial steal." Certainly this treatment appears to have little clinical effect and has been abandoned. Conversely, there is no evidence that a reduction in pCO_2 would be advantageous, and this might reduce the pressure gradient from nearby normal areas.

More recently anticoagulants, fibrinolysins, and desludging agents (low molecular weight dextrans) have been advocated. Anticoagulants do not restore blood flow to a thrombosed vessel and do not improve flow in partially occluded vessels; they are dangerous if used in patients with unsuspected hemorrhage and are probably better avoided. This of course in no way belittles their value when used prophylactically in suitable patients. At the moment fibrinolysins are too difficult to control for routine use and their value has yet to be demonstrated.

Plasma expanders, such as low molecular weight dextrans, have many theoretical advantages but are not widely used because of the necessity of intravenous infusion and lack of evidence of its value which is probably due to the difficulty in carrying out suitable trials. They do not cause bleeding in the intact vascular system and certainly help to maintain blood flow in critical situations. A small increase in cerebral blood flow has been demonstrated during infusion with plasma expanders but this may be partly due to the reduced oxygen carrying capacity. Theoretically they would be best used immediately following an embolus while collateral channels are opening up but a controlled experiment in cats following occlusion of the middle cerebral artery did not show a significant difference in the size of the resulting infarct.

Extracranial cerebrovascular disease and the indications for surgery. The relationship between the stenosis or occlusion of the extracranial part of the cerebral blood vessels and cerebral infarction or ischemia was recognized over a century ago[1] but it was not until the advent of arteriography that the extent of extracranial cerebral vascular disease became apparent. These lesions give rise to cerebral damage in two ways: as a source of emboli and by reduction in blood flow.[1-3]

A great deal of work has been done in the

last few years and it is now known that stenosis or even occlusion of a major vessel in the neck may occur without neurological deficit,[4] it is a common finding post mortem in normal subjects[11,2] and in practice there may be difficulty in relating the clinical to the radiological findings.[7,1]

Blood flow studies have shown that a very considerable reduction in the lumen of an artery is necessary before flow is affected. Brice and associates[34] found that with a mean carotid lumen of 30 mm (range 17 to 55) a reduction to 5 mm was required before flow was affected and that significant impairment did not occur until the lumen was reduced to 2 mm.[3] Lowe[21] has pointed out that the extracranial vessels account for only 10 per cent of the total cerebrovascular resistance and that occlusion of three of the four major vessels or a severe stenosis to about 10 per cent of all four vessels would be required to increase the extracranial cerebrovascular resistance to equal the intracranial cerebrovascular resistance. Mann and colleagues[25] found that a 50 per cent reduction in lumen had no effect on flow and that a 90 per cent reduction caused a 50 per cent fall in flow. A pressure gradient does not necessarily mean a fall in flow[40] and a reduced or an absent carotid pulse found clinically does not necessarily mean complete occlusion. Ideally both the blood flow and the pressure gradient are needed for full evaluation of the local hemodynamics.[31] These studies have shown that many carotid stenoses are not significant in terms of vessel flow at normal perfusion pressures but hypotension may profoundly affect this.

Emboli from atheromatous lesions in the neck vessels may be of three types: platelet aggregations which may give rise to transient ischemic attacks (these have been seen traversing the retinal circulation),[10,37] mural thrombi and atheromatous debris, both of which are more likely to cause established strokes. Since many of these lesions are accessible to surgery, endarterectomy has been widely practiced for lesions of all degrees of severity from atheromatous irregularity to complete obstruction. The object of the procedure is to remove a source of microemboli or to relieve a significant stenosis in order to improve the blood supply to the cerebrovascular pool especially when there is evidence of occlusive disease in the other main vessels and this might also forestall the development of complete obstruction. Surgery is usually considered to be prophylactic against further transient ischemic attacks or the development of an established stroke but is seldom associated with much improvement in the neurological state over that which might be expected in the natural history of the disease. Most series, however, include a few patients who appear to make considerable improvement as a direct result of an operation. Against this must be set the not inconsiderable morbidity and small mortality rate directly attributable to operative intervention.

In these circumstances it is necessary to know something of the natural history of the condition. Published data on this are very scarce but in a recent paper Bradshaw and Casey[13] reported satisfactory neurological progress in 60 per cent of the patients with stenosis and 45 per cent of those with occlusion. Thompson[33] found that age, hypertension and evidence of small vessel disease were important adverse factors in determining prognosis.

It is also necessary to know which patients are unlikely to do well at or following operation. It would appear that disobliteration of occluded vessels produces no benefit unless done within a few hours of occlusion. Prognosis also appears to vary inversely with the degree of persisting neurological deficit and the age of the patient.[39] The ideal patient for surgery is therefore young, suffering from transient ischemic attacks clearly attributable to a stenotic lesion in the carotid artery and without persisting neurological signs, whereas the elderly hypertensive patient with a complete occlusion and ipsilateral completed stroke should probably not be submitted to surgery. The difficulty arises over the vast majority of patients who lie between these two extremes. The decision as to whether a patient should be investigated *is a matter* of experience in which the available facilities and expertise are a major consideration.[31]

Four vessel angiography is, of course, necessary before the problem can be fully assessed and it is important to visualize the origins of the vessels from the arch of

the aorta. There is no point in submitting a patient to angiography if an operation is contraindicated on other grounds or if the patient is unwilling to proceed to surgery.

Summary

Physiological and anatomical features of the cerebral vascular system already discussed explain why there is an inconsistent relationship between degenerative arterial disease in the major neck vessels and cerebral ischemia. It is probably the state of the smaller vessels at or above the circle of Willis which determines the site of an ischemic lesion not due to emboli.[8,9] For example, when there is a stenosis of the carotid artery, infarction is much more likely in the ipsilateral middle cerebral artery territory if there is congenital hypoplasia of the posterior communicating artery on the same side. Disease above the circle of Willis is likely to have a profound effect on cellular perfusion so that a marked reduction in cortex perfusion, especially if asymmetrical between the hemispheres, is good evidence of disease at or above the circle of Willis. It has been shown that atheromatous lesions in the carotid arteries have no constant effect on cerebral cortex perfusion rates[14] and that removal of a stenosis thought to be significant in terms of vessel blood flow has no constant effect on cellular perfusion. From a small series in which pre- and postoperative cortex perfusion rates were estimated it would appear that those patients with markedly reduced or asymmetrical perfusion rates were less likely to profit from surgical intervention. An operation on the carotid bifurcation is much less likely to benefit the patient if the final common pathway of blood to the cells is severely compromised.

Surgery is most suitable, therefore, for patients whose symptoms are likely to be due to emboli, who preferably have little or no persisting neurological deficit, and who also have no evidence of significant small vessel disease. Preliminary results suggest that cerebral blood flow measurements can provide additional information about the state of the small vessels and thus may be important in determining both prognosis and suitability for operation. Surgery may also be indicated for those patients who have such extensive occlusive disease that the over-all supply of blood to the cerebral pool is jeopardized. It should be borne in mind, however, that emboli are not the only cause of strokes or transient ischemic attacks in the presence of extracranial cerebral vascular disease and there may be surprisingly little neurological deficit in patients with only one patent vessel. This is illustrated by the case report by Gull[10] which starts with the following sentence: "It scarcely seems credible that a person shall live in the enjoyment of her faculties and in comparative health with all the major vessels of the head and neck, except the left subclavian, closed at their origin from the arch of the aorta."

REFERENCES

1. Registrar General: Statistical Review, 1965.
2. Lassen, N.: Cerebral blood flow and oxygen consumption in man, Physiol. Rev. 39:183, 1959.
3. Bayliss, W. M.: On the local reaction of the arterial wall to changes in internal pressure, J. Physiol. 28:220, 1902.
4. Meyer, J. S., Handa, J., Huber, P., and Yoshida, K.: Effect of hypotension on internal and external carotid blood flow, J. Neurosurg. 23:191, 1965.
5. Severinghaus, J. W., Chiodi, H., Eger, E. I., Brandstater, B., and Hornbein, T. F.: Cerebral blood flow in man at high altitude, Circulation Res. 19:274, 1966.
6. Harper, A. M.: Autoregulation of cerebral blood flow: influence of arterial blood pressure on the blood flow through the cerebral cortex, J. Neurol. Neurosurg. & Psychiat. 29:398, 1966.
7. Häggendal, E., and Johansson, B.: Effect of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow and autoregulation in dogs, Acta physiol. Scandinav. Suppl. 66:27, 1965.
8. Meyer, J. S., and Denny-Brown, D.: The cerebral circulation. I. Factors influencing collateral blood flow, Neurology 7:447, 1957.
9. Sundt, T. M., Waltz, A. G., and Sayre, G. P.: Experimental cerebral infarction: modification by treatment with hemodiluting, hemoconcentrating and dehydrating agents, J. Neurosurg. 27:46, 1967.
10. Gull, W.: Thickening and dilation of the arch of the aorta with occlusion of the innominate and left carotid: atrophic softening of the brain, Guy's Hosp. Rep. (Series 3) 1:12, 1855.
11. Fisher, C. M.: Occlusion of the carotid arteries, Arch. Neurol. & Psychiat. 72:187, 1954.
12. Millikan, C. H.: The pathogenesis of transient focal cerebral ischemia, Circulation 32:438, 1965.
13. Millikan, C. H., and Siekert, R. G.: Studies in cerebrovascular disease. I. Syndromes of intermittent insufficiency of the basilar arterial system, Proc. Staff Meet. Mayo Clin. 30:61, 1955.

14. Fisher C. M. Occlusion of the internal carotid artery Arch. Neurol. & Psychiat. 65:346, 1951
15. Battacharji, S. K. Hutchinson, E. C., and M Call, A. J : Stenosis and occlusion of vessels in cerebral infarction, Brit. M J 3:270, 1967
16. Schwartz, C. J and Mitchell, J R. A. Atheroma of the carotid and vertebral arterial systems, Brit. M J 2 1057 1961
17. Muller R., Greitz, T Liliequist, B., and Hellstrőm, L Aortocervical angiography in occlusive cerebrovascular disease Neurology 14 136, 1964.
18. De Bakey M E., Crawford, E S Cooley D A., Morris, G. C Garrett, H. E., and Fields, W S Cerebral arterial insufficiency Ann Surg 161:921, 1965
19. Gurdjian, E. S., and Thomas, L M Evaluation and indications for surgery in extracranial cerebrovascular disease, J Neurosurg 26:235 1967
20. Brice, J G Dowsett, D J and Lowe, R D Haemodynamic effects of carotid artery stenosis, Brit. M J 2 1363, 1964.
21. Lowe R. D Adaption of the circle of Willis to occlusion of the carotid or vertebral artery its implication in carotico-vertebral stenosis Lancet 1:395 1962.
22. Mann, F C Herrick, J F Essex, H. E and Baldes, E G. The effect on blood flow on decreasing the lumen of blood vessel, Surgery 4:249 1938.
23. Cannon, J A Lobprels, E L Herrold, G and Frankenberg, H. L. Experience with new electromagnetic flow meter for use in blood flow determinations in surgery Ann. Surg 152:635 1960.
24. Dellin A and Ekestrom, S Evaluation of reconstructive surgery for arterial stenoses from intraoperative determinations of flow pressure and resistance, Acta chir Scandinav 130:35 1965.
25. Fisher C M Observations of the fundus oculi in transient monocular blindness, Neurology 9:333 1959
26. Russell, R. W R Observations on the retinal blood vessels in monocular blindness, Lancet 2 1422 1961
27. Ashby M Oakley N Lorentz, I and Scott, D Recurrent transient monocular blindness, Brit. M J 2:894 1963.
28. Bradshaw P and Casey E. Outcome of medically treated stroke associated with stenosis or occlusion of the internal carotid artery Brit M J 1:201 1967
29. Thompson, J L. G. Prognosis in disease of major cerebral vessels, Post-Grad M. J 37:437 1961.
30. Gurdjian, E. S Darmody W R., Lindner D W and Thomas, L M The fate of patients with carotid and vertical artery surgery for stenosis or occlusion, Surg Gynec. & Obst. 121:326, 1965
31. Marshall, J L. The use and abuse of cerebral angiography in the diagnosis of strokes, AM. HEART J 74 145 1967
32. Cronqvist, S. Total angiography in the evaluation of cerebrovascular disease a correlative study of aorto-cervical and selective cerebral angiography Brit. J Radiol 39:805 1966
33. Dickinson, C J Functional efficiency of the circle of Willis, Brit M J 1:858, 1961
34. O'Brien, M D Veall, N Luck, R J and Irvine, W T Cerebral cortex perfusion rates in extracranial cerebrovascular disease and the effect of operation, Lancet 2:392, 1967
35. Shalit, M N Shimojyo, S. Reinmuth, O M and Scheinberg, P Carbon dioxide and cerebral circulatory control. Part I. The extravascular effect, Arch. Neurol. 17:290, 1967
36. Shalit, M N Shimojyo, S., Reinmuth, O. M and Scheinberg, P Carbon dioxide and cerebral circulatory control. Part II The intravascular effect, Arch. Neurol. 17:337 1967
37. Shalit, M N Shimojyo, S., Reinmuth, O M., and Scheinberg, P Carbon dioxide and cerebral circulatory control. Part III The effect of brain stem lesions Arch Neurol. 17:342, 1967

Surgical treatment of valvular heart disease

Part VI. Aortic valve surgery

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Before the advent of open-cardiac surgery, little could be done to relieve the disabling signs and symptoms of aortic valvular insufficiency or stenosis. Aortic insufficiency, characterized by slowly progressive deterioration and refractory congestive heart failure, often advanced to massive enlargement of the heart (cor bovinum) before death occurred. Aortic stenosis was characterized by a more rapid deterioration from the onset of congestive heart failure, pulmonary edema, decreased exercise tolerance to ventricular arrhythmia, and sudden death. All those with aortic valvular disease lived under the constant shadow of calcific embolization and bacterial endocarditis with consequent mycotic embolus, leaflet perforation, and massive acute valvular insufficiency.

Nonvisual methods of transaortic or transventricular dilatation of the stenotic aortic valve met with only occasional success. The Hufnagel ball valve afforded partial relief of aortic insufficiency before cardiopulmonary bypass was available.[1] It was inserted into the aorta distal to the left subclavian artery, but it corrected insufficiency only in that portion of the cardiac output which passed beyond the vessels to the head and upper extremities. Because the coronary arteries fill in diastole, the persistent aortic insufficiency did little to improve the nourishment of the heart.

Cardiopulmonary bypass permitted a direct attack on the aortic valve. Direct vision valvulotomy and removal of calcification was accomplished with partial relief of stenosis. Recalcification and restenosis regularly occurred after surgery.

Aortic insufficiency was treated with Teflon and Ivalon bolsters to support the valve leaflets[2] and conversion of the normally tricuspid valve to a bicuspid configuration by obliteration of the noncoronary cusp and prosthetic replacement of a single cusp.

None of these procedures were ultimately successful. Only Starr's placement of a prosthetic ball valve in the subcoronary (anatomic) position provided a significant therapeutic result.[3] Once anatomic placement of a prosthetic valve had been ac-

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complished a large variety of valves (sutureless, lenticular and leaflet) were devised and homograft and heterograft valve replacement was undertaken.

Etiology of aortic valve disease

Hemodynamically significant aortic stenosis results from arteriosclerotic or rheumatic destruction or congenital malformation (bicuspid) of the valve with superimposed dense calcification. Aortic insufficiency also follows rheumatic and arteriosclerotic valvular destruction. It occurs with aneurysm of the ascending aorta caused by cystic medial necrosis (Marfan's disease) arteriosclerosis syphilis, and dissection of the aorta. The aortic insufficiency of the ascending aortic aneurysm is characterized by a dilated aortic annulus with relatively normal valve leaflets.

Clinical manifestations and the role of diagnostic procedures

In the presence of severe aortic valvular disease, angiocardiography and cardiac catheterization procedures may have a higher mortality rate than replacement surgery. If little question exists concerning the cause of the symptoms requiring treatment then those diagnostic procedures should be avoided. The diagnosis and appropriate therapeutic decisions can usually be made on clinical grounds alone. Delay is to be avoided especially for the aortic stenotic whose penchant for sudden death makes delay hazardous. Only when the hemodynamic importance of the valvular lesion is in question or when the possibility of infundibular or supravalvular stenosis exists, is a major diagnostic procedure indicated.

Angina pectoris, congestive heart failure, syncope, and pulmonary edema are compelling indications for aortic valve surgery. Angina may be an indication for coronary angiography in the presence of aortic valve disease. The angina may result from the aortic valve lesion, coronary artery disease, or a combination of the two and may be completely relieved by valve replacement. Ventricular arrhythmia is a treacherous manifestation of aortic stenosis and may cause sudden death even in a largely asymptomatic patient.

Surgical repair

Almost all aortic valve surgery involves replacement of the diseased valve with either a prosthesis (usually of the ball valve variety) or a homograft. Prosthetic valves are readily available in a wide variety of sizes and are relatively easy to insert. Valvular competence is intrinsic to prosthetic valve design and is not dependent upon the surgeon's ability to narrow a dilated aortic annulus. Prosthetic valve replacement is therefore preferred for lesions associated with a dilated aortic annulus, while either prosthetic or homograft replacement is suitable for lesions with a normal-size aortic annulus. Hog and calf aortic valve heterografts are in clinical evaluation, and their long term utility has not been established.

Valve replacement can be accomplished with a mortality rate less than 15 per cent with either prosthetics or grafts. The older ball valves with a silicone rubber ball and a bare steel cage have been associated with the following major difficulties.

1 Thrombus formation and an excessive incidence of embolization have been observed.

2 Ball variance or change in size and configuration of the silicone rubber ball has been reported. Major surface damage and splitting have occurred. These balls have been found to contain lakes of brownish, semiliquid lipid material the expansion and contraction of which may be the cause of the splitting of the ball. These structural changes produce malfunction of the prosthesis with insufficiency and rarely escape of the ball from the valve cage with consequent sudden aortic insufficiency and death. Ten per cent of Starr's implants have had some manifestation of the variant ball syndrome. Diagnosis is based on change in the prosthetic valve sound. The opening sound loses its sharp click, becomes muffled and may even disappear. A regurgitant sound may also appear. Phonocardiography performed shortly after implant and repeated at intervals, has been useful in documenting the change in valve sounds.

3 There has been detachment of the sewing ring from the aortic annulus with insufficiency peripheral to the prosthesis.

4 Persistent gradient after valve implantation has occurred which is caused by a small orifice in the prosthesis or a narrow ascending aorta that encroaches upon the ball and cage during systole

5 There has been a need for chronic anticoagulation which is often accompanied by complications

6 Chronic low-grade hemolysis or hemolytic anemia has been observed

7 The sutureless valves have had a significant incidence of leak between the prosthetic valve ring and the aortic valve annulus. Present utilization of this prosthesis is limited

All metal surfaces of the most recent Starr Edwards prosthesis are Dacron-covered A hollow titanium ball has replaced the silicone ball The incidence of thromboembolism and ball variance may be reduced by these modifications. The problem of systolic gradient may be accentuated in some instances when the ingrowth of tissue into the cloth of the prosthesis further narrows the valve orifice. Because of the presumed reduction of ball variance Starr has recommended that all of the older valves be electively replaced with the newer variety

Homo- and heterograft valves

Several medical centers have implanted large numbers of aortic valve homografts [6] Procurement of an adequate number of normal sterile valves has presented a supply problem especially regarding the lack of consistent availability of a variety of valve sizes. These deficiencies may be solved by a bank of aortic valve heterografts, possibly supplied commercially as are mechanical prostheses.

Homo- and heterografting can be accomplished with an operative mortality rate similar to that of a series of prosthetic grafts, though operating time is unquestionably longer [7] Both heterografts and the more commonly done homografts have prolonged patients lives for a period of 3 to 4 years, as do the prosthetic valves. The tissue valves have not had the post operative hemolysis and thrombus formation which accompanies the prosthetics. Neither peripheral nor coronary artery emboli have occurred, and anticoagulation has been unnecessary No pressure gradient across the valve exists.

Late cusp failure with loss of attachment to the valve supports, and resultant severe aortic insufficiency have occurred in addition to the very mild aortic insufficiency which constantly accompanies aortic homoheterografts. While 90 per cent of all those patients who show successful results three months after valve grafting continue to do so for 1 to 4½ years,[8] late stenosis and incompetence have sometimes been seen. These symptoms may result from extensive calcification of the graft and the adjacent aortic wall both of which have occurred 2½ to 3 years after implantation.[9] Bacterial endocarditis can occur on aortic valve grafts but it is easier to eradicate than an infection of a prosthetic valve. Late deterioration of homoheterografts is generally amenable to correction by a second operative procedure. Prosthetic valve complications tend to be devastating or immediately fatal

Summary

Aortic valve replacement can be readily accomplished either with a prosthetic valve or a homo- or heterograft placed in the subcoronary position. The operative mortality rate of all procedures is under fifteen per cent. Complications of thrombosis, embolization and ball variance have plagued the prosthetic ball valve. Fibrosis of valve leaflets, calcification and late stenosis and insufficiency of the homo- and heterografts have been reported The ideal aortic valve replacement has not yet been devised but very satisfactory clinical relief of aortic valve disease is now possible with either prosthetic or grafted valves.

REFERENCES

1 Hufnagel, C. A Harvey W P Rabil, P J and McDermott, T F Surgical correction of aortic insufficiency Surgery 35:673, 1954

2. Bahnson H T Spencer F C., Busse E. F G., and Davis, F W J Cusp replacement and coronary-artery perfusion in open operations on the aortic valve, Ann. S. 152:494 1960.

3 Starr A., Edwards, M L McCord, C. W and Griswold H. E. Aortic replacement: clinical experience with semirigid ball-valve prosthesis, Circulation 27 779 1963.

4 Herr R. H Kloster F E., Seral, Y and Starr A Diagnosis and management of "ball vari-

ance following aortic valve replacement, Circulation 26 141 1967
5 Ross, D Homotransplantation of the aortic valve in the subcoronary position, J Thoracic & Cardiovas Surg 47 713 1964.
6. Barratt-Boyes, B. G. Homograft aortic valve replacement in aortic incompetence and stenosis, Thorax 19 131 1964
7 Binet, J P Duran, C. G Carpentier A., and Langlois, J Heterologous aortic valve transplantation, Lancet II 1275 1965
8 Ross, D N Aortic valve replacement, Lancet II:461, 1966.
9 Hudson, R. E. B Pathology of the human aortic valve homograft, Brit. Heart J 28:291 1966.

Annotations

Fundal changes in cardiac arrest and their significance

M jor problem when tre ting patient th cardiac arrest are the decisions when t persev ere hen ther is no pparent immediat response, or when treat ment ll be t no ail or t best ll onl produce decerebrate existenc Not infrequentl the precise length of time that state of total circulatory arrest has existed is not know n before effectiv treatment is instituted The maximum time between arrest of the cerebral circulation and death of the br in is little over four min tes in previously healthy patient but obviously here previous h poxemia, erebral ischemia, or severe hypotension ha occurred then the four m te margi is severely curta led. I these situations even should an effectiv cerebral ci lation be restored thi the four min te period the brain ma will be irretrievably damaged and the patient ll die Persistence of resuscitation in these circumstances is undesirable. Should the patient be artificially entilated and ha ing such medication as t bocurarine at the time of the arrest or such therapy be given during treatment of the cardiac arrest then there may be no obvious physical sign of death for some considerable time Reliable elec troencephalogram (EEG) recording nd on site in terpretation of the record so obtained is a facility not usually ilable t the time nd plac of the ardiac arrest There is need t know both when to persist in the fac of no immediat response to tre tment and when to stop treatment

Bouchet described the retinal changes that occu t death hen the f ndi are examined ophthalmo scopically Laher[1] proposed that the ey signs should gi a guide to resuscitability though i the context of medicine at this time, this referred more t arti ficial ventilation rather tha artificial systole by cardiac massage. However little notice appears to ha e been taken of this suggestion and part from the medicolegal implications regarding certifying the actual time of death the ey signs t death ha been largely of academic interest.

Salisbury and M hin investigated the problem experimentally and they showed that when frag mentation of the column of blood thin the retinal vessels occurred the animal died therefore, they proposed that this should be a guide for determining whether to resuscitate. Kevorkian[4] reported that such retinal changes occurred in ma and were associated with the death of the patient. This report contained descriptions of observations made on two patients in cardiac arrest at normothermia and sev eral others occurring t hypothermia though the retinal changes were modified by hypothermia. How ever the significance and prognostic value of these observations ha not as yet been determined quantitatively n man.

What actually is seen depends upon the state of the patient Where hypotension or hypoxemia are present the first sign is substa tial slowing of blood flow in the retinal essels the arteries appear ex tremely thin but the red line of blood within them is continuous, the eins ppear much wider and darker than usual and the column of blood appears alm mov ng gra ular flow and these are similar t the ppearances that Salisbury found in some of his experiments.

The next stage is the f agmentation of the column of blood thin the eins, the fragme ts, initially close together move lowly towards the optic disc If the patient has gross cerebral circulatory insuf ficiency this ppearance may precede the actual ardiac arrest In a hypotensi hypoxic patient this appearance may develop within 30 seconds after cardiac arrest has been detected on an oscilloscope trace of the electrocardiogram (ECG) The next stage is when the drifting movement of the clumps of blood cells in the eins toward the optic disc ceases and movement becomes random. The clumps bump aga nst each other—the so-called rail roading or attle trucking effect. This fragmen tation of the blood colum occurs in both arteries and eins

The optical definition particularly of the arteries becomes less good as though parts of the arteries are moving towards the observer and then back into focus again This movement is slow nd takes up t five seconds between being in focus, out of focus, and back again. Salisbury[2] suggested that this may be due t drying of the eye, but it occurs even in well lubricated eyes, furthermore in previously ery shocked patients it ppears too rapidly for drying to be the cause. The most likely cause ould be irregu lar edema formation constricting the now toneless essels and this rapid shifting edema fluid may occasionally be seen on the surface of the retina. A fuller description of the f ndal changes may be found in Duke Elder s[4] reference ork but t must be tressed that the appearances t this time are very characteristic and easy to observe as the pupils are idely dilated at this tage.

I a series of 102 personally ttended cardiac arrests, this sign of random oscillation of clumps of blood cells within the retinal vessels has now been

observed on 21 occasions. For technical reasons fundal examinations were not carried out at all attendances of the cardiac arrests. Of the 102 cardiac arrests, the circulation was restored to the prearrest state on 50 occasions, but in the 21 patients in which the fundal changes were observed 20 did not succeed in getting their circulation restarted, and the one successful restoration of circulation in this group occurred in a child, and she became decerebrate as a result of the arrest. If the fundal changes had no significance then the likely expectation of restoring circulation would be 10 patients of the 21. On statistical grounds this difference between expected and observed results is highly significant (P less than 0.01).

The most likely explanation for the association between the observed fundal appearances and failure to restore the circulation is that edema and swelling of the retinal cells is occurring, and it is this which is causing the disruption of the column of blood within the retinal vessels by irregular compression of the vessels. Phylogenetically, the retina is an extension of the brain and what is seen occurring in the retina may well be occurring in the brain, and when this stage of cell damage is reached the neurones are dying. Hence also the vasomotor center is likely to be irreparably damaged as well as the cerebral cortex.

It may be concluded that the presence of this physical sign is indicative of cerebral death and when seen, resuscitation should be abandoned, otherwise decerebrate survival is the best that may be expected. The converse interpretation that is the brain is not dead until this sign is seen may not be true as that it may have occurred and then subsequently sufficiently good circulation be obtained by artificial systole that the hemodynamic pressure generated is greater than the edema pressure and so the column of blood within the vessels is reformed. At this stage the fundus may now appear normal. However the damage to the retinal and brain cells has already occurred. In the absence of other signs of death, it is still reasonable to persist with resuscitation in the cardiac arrest situation until these fundal changes are seen or the patient responds to treatment.

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REFERENCES

1. Bouchet, E.: Atlas d'opthalmoscopie Medicale et de cérébroscopie, Paris, 1876, J. B. Baillière et Fils, pp. 56-57.
2. Usher, C. H.: Observations on retinal blood stream at time of death, Ophth. Rev. 15:339, 1896.
3. Salisbury, C. R., and Melvin, G.: Ophthalmoscopic signs of death, Brit. M. J. 1:1249, 1936.
4. Kevorkian, J.: Rapid and accurate ophthalmoscopic determination of circulatory arrest, J.A.M.A. 164:1660, 1957.
5. John, P. O. L.: Railroading in retinal vessels, Brit. M. J. 4:357, 1967.
6. Duke-Elder, Sir Stewart: The fundus in sleep, cardiac arrest, and death. System of opthalmology, London, 1962, Henry Kimpton, Vol. VII.
7. Tomlin, P. J.: Railroading in retinal vessels, Brit. M. J. 4:722, 1967.

Cardiac involvement in epidemic dropsy (Argemone mexicana poisoning)

Epidemic dropsy was first described in Calcutta in 1877. Since then many outbreaks have occurred in India and also occasionally in Mauritius, Fiji, and South Africa.

It is now well established that epidemic dropsy results from the adulteration of edible oils used for cooking, with the oil expressed from seeds of *Argemone mexicana* (the Mexican prickly yellow poppy). The alkaloid sanguinarine is considered to be the main toxic component of argemone oil. The clinical picture of epidemic dropsy has been reproduced in human volunteers by the administration of argemone oil and of sanguinarine. Histologically similar changes in the heart have been produced in experimental animals given argemone oil.

The incidence of cardiac failure and deaths has varied considerably from epidemic to epidemic. In eight outbreaks reported from various parts of India over the past 40 years, the mortality rate ranged from 4 to 20 per cent. Those with moderate cardiac involvement complain of palpitation and dyspnea upon exertion, they have heart rates of 90 to 120 per minute, normal systolic blood pressure, wide pulse pressure, and perhaps signs of right heart failure such as hepatomegaly and elevated jugular venous pressure. Those with severe heart involvement suffer from orthopnea or paroxysmal dyspnea, have heart rates about 130 per minute, generalized edema, and falling systolic blood pressure. In such patients death may occur suddenly or follow acute pulmonary edema.

During the recent outbreak in Bombay, 27 indi-

...duals suffering from epidemic dropsy were studied at the Lokmanya Tilak Municipal General Hospital. Seven patients had cardiac failure, and three of them died.

Edema of the lower limbs is a very constant finding. Petechiae and cutaneous telangiectasis may be present, and the edematous skin is warm and erythematous; these features distinguish epidemic dropsy from most other causes of pitting pedal edema.

Sinus tachycardia has been the sole electrocardiographic abnormality in the majority of reported cases. ST segment deviation and flattening or inversion of the T wave were noted in a few instances and were observed in t of our patients. One case with atrial fibrillation has been reported.

The most prominent and typical histological feature is the enormous dilatation of capillaries in tissues throughout the body. This is well seen in the myocardium and epicardium. Other microscopic changes in the myocardium include interstitial edema, foci of mononuclear cell infiltration and fatty degeneration, hydropic degeneration, necrosis, or hypertrophy of muscle fibers.

In those who survive, recovery is slow; edema and tachycardia usually persist for several weeks. However, it is generally believed that permanent cardiac damage does not result.

In addition to routine therapeutic measures for cardiac failure, other forms of therapy, such as ephedrine, British antilewisite, corticosteroids, and cysteine have been tried with no proved efficacy.

A simple chemical test to detect the presence of argemone oil in edible oils has facilitated public health measures to locate and eliminate sources of contamination.

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REFERENCES

1. Lal, R. B., and Roy, S. C.: Investigations into the epidemiology of epidemic dropsy, Indian J. M. Res. 25:1, 1937.
2. Lal, R. B., and Roy, S. C.: Investigations into the epidemiology of epidemic dropsy, Indian J. M. Res. 25:239, 1937.
3. Chopra, R. N., Pasricha, C. L., Goyal, R. K., Lal, S., and Sen, A. K.: The experimental production of the syndrome of epidemic dropsy in man, Indian M. Gaz. 74:193, 1939.
4. Chaudhuri, R. N.: Clinical and experimental research—Epidemic dropsy, Bull. Cal. Sch. Trop. Med. 7:157, 1959.
5. Chopra, R. N., Chaudhuri, R. N., and De, N.: Electrocardiographic changes in epidemic dropsy, Indian M. Gaz. 72:1, 1937.
6. Desai, R. A., and Mohile, G. B.: Epidemic dropsy in Nadiad, J. Indian M. A. 24:248, 1955.
7. Shankar, G., and De, M. N.: The pathology of epidemic dropsy, Indian J. M. Res. 19:169, 1931.
8. De, M. N., and Chatterjee, K. D.: Pathology of epidemic dropsy, Indian M. Gaz. 70:489, 1935.
9. Chaudhuri, R. N., and Chakravarty, N. K.: Treatment of epidemic dropsy, Indian M. Gaz. 85:165, 1950.
10. Shah, M. J., and Lewis, R. A.: Epidemic dropsy. Nadiad epidemic: Observations on serum proteins and cortisone therapy, J. Indian M. A. 24:245, 1955.
11. Chakravarti, R. N., Chaudhuri, R. N., and Chakravarty, N. K.: Epidemic dropsy: a new test for argemone oil, Indian M. Gaz. 85:344, 1950.

What is a β blocker?

Amid the ever-increasing complexities of modern medicine it is inevitable that short, easily remembered labels become everyday catchphrases. In many ways, β-blocker is a most acceptable label for a new and highly specific class of drugs since it implies much of the underlying theory. In clinical practice β-blockade is of value in the management of angina pectoris and a variety of cardiac arrhythmias. It is the purpose of this article to provide a brief outline of the theory of adrenergic β-receptor antagonism and to suggest the specifications necessary for the use of this terminology.

A pharmacologist would probably define a β-blocker as an agent which produced a specific and competitive antagonism at the β-receptor site. But how many people understand the term β-receptor site? Ever since the pioneer studies of Barger and Dale there has been considerable doubt about the true identity of the transmitter substances released at the terminals of nerve fibers in the sympathetic division of the autonomic nervous system. In many experiments it was impossible to reproduce exactly the effects of sympathetic nerve stimulation by injections of pure epinephrine or norepinephrine. This situation led Cannon and Rosenblueth[1] to coin the term sympathin and to suggest that it existed in two forms, i.e., excitor (sympathin E) and inhibitor (sympathin I). The confusion persisted even though norepinephrine was firmly established as the substance liberated at sympathetic nerve terminals.

I 1948, Ahlquist[3] made the revolutionary suggestion that there were two types of *receptor* site rather than two transmitter substances in the sympathetic innervation. On the basis of study with a variety of sympathomimetic amines, it was possible to arrange their order of potency into two entirely separate patterns on preparations including cardiac and smooth muscle and various peripheral organ systems. I one series epinephrine was the most potent and isoproterenol the least potent in the other isoproterenol was most potent and norepinephrine least potent (Table I). The two types of receptor were arbitrarily designated α and β. Activation of β-receptors results in stimulation of cardiac muscle and the inhibition of muscle in skeletal blood vessels, the bronchi, intestine, and uterus. Activation of α-receptors results in stimulation of muscle in peripheral blood vessels the ureter and the iris. Most sympathomimetic amines are able to stimulate both types of receptor although there is usually greater affinity for one type. However isoproterenol is unique in that it combines only with β-receptors, under normal conditions. This explains the numerous references to the use of isoproterenol in experiments concerned with β-blockade. Despite this pharmacological convenience, it must be remembered that *norepinephrine* is the natural transmitter in the heart. Even though norepinephrine is last in Ahlquist order of potency its capacity to stimulate cardiac β-receptors is of vital importance.

Additional support for the α- and β-receptor concept was derived from the fact that adrenergic antagonists known at that time blocked only α-receptor responses. Much greater support, however came from the discovery that dichloroisoprenaline (DCI) selectively blocked the β-receptors.[6,7] The interesting aspect of DCI was that it offered not only specific but also *competitive* antagonism at the β-receptor site.

By specific antagonism is meant blockade of stimulation through particular receptor site. For example, it is insufficient to consider the end response alone g tachycardia. Isoprenaline and atropine both produce an increase in heart rate so does an excess of calcium ions yet only isoprenaline is specific stimulant of cardiac β-receptors and DCI is specific in the sense that it, too, seeks out β-receptors while not interfering with the effect of atropine or calcium. A competitive antagonist may be defined as one which moves the dose response curve to the right when considering the interaction between a given stimulant and receptor site. DCI also meets this criterion. Possession of specific and competitive blocking properties is often accompanied by close structural similarity to the compounds producing stimulation. I some cases this means that the antagonist also shows some stimulant activity. This is the case with DCI.

I the following years two substances related to DCI have been introduced to clinical medicine pronethalol, which has less β-stimulant property and propranolol which has none. All three compounds share the property of producing both specific and competitive blockade at all the recognized β-receptor sites. Indeed the β-blocking drugs are so specific that investigators have lately sought to classify previously undesignated adrenergic receptors on the basis of antagonism. But there are inherent dangers in such circular arguments as pointed out by Moran.[10] New drugs may be classified as β-adrenergic blocking agents because they block an effect previously termed β-effect, perhaps merely because it is blocked by an older established β-adrenergic blocking drug. This may be illustrated in the case of N-isopropylmethoxamine which may be shown to antagonize the effects of catecholamines on lipolysis. Previous investigations had shown that this effect was blocked by DCI and therefore it was regarded as β-effect. Yet careful comparison of the fat-mobilizing potencies of sympathomimetic amines shows that there is little difference in the potency of isoproterenol norepinephrine, and epinephrine, that others have little if any effect, and that the slope of antagonism dose-response curves is much shallower than that for chronotropic cardiac responses.[11] It cannot be too strongly emphasized that the demonstration of antagonism which may be overcome by increasing the concentration of adrenergic β-receptor stimulant does not constitute proof of β-blockade. Nor on the other hand, may it be assumed that, once specific and competitive β-blocking properties have been proved for given compound, any other observed biological response is necessarily due to β-blockade.

How then should one test new agent before being able to attach the label β-blocker with confidence? It would be desirable to show specific and competitive antagonism in all situations in which β-receptors are involved. Yet this is time consuming process and may require techniques and facilities not available in every laboratory. Results obtained in systems in vitro may not necessarily be transferable either to anesthetized animals or then again to conscious animals and man. Some physiologists hold the belief that anesthetized dogs give the best indication of what may happen in man. Levy and Ahlquist described test in which potential β-blockers could convert the usual depressor response to ethylnorepinephrine into a pressor response However this was inadequate since similar reversal was produced by any pressor agent, eg phenylephrine. Other workers have relied upon the reduction in tachycardia and vasodilation produced by isoproterenol in anesthetized cats as their index of β-blockade. Whole-animal techniques, however may give results modified by reflex responses. Most

Table I. Potency of sympathomimetic amines (after Ahlquist)[3]

Order of activity	Vasoconstriction (α-receptor)	Tachycardia (β-receptor)
1	Epinephrine	Isoproterenol
2	Norepinephrine	Methylepinephrine
3	Methylnorepinephrine	Epinephrine
4	Methylepinephrine	Methylnorepinephrine
5	Isoproterenol	Norepinephrine

attract is the method h h segme t of right nd left tria mou ted the same bath This perm t evaluation of antagonism of both chronotropic nd inotropic responses ell showing up other properties on ardiac muscle Yet t gives no int m tion of other possible effect g socon triction ith methoxamine

F om the iewpoint of card log t β-blocker must be shown spec fic ll t antagonize the effects of mpathet tim lation part larly the heart Demonstration of isoproterenol ntagonism i dogs or epinephrine tagonism solated tria is relevant but not exclusively dom nant the l e l t on where there is excess sympathet drive For this re son β-blocks should be be pable of reduc ng he m ardial responses t lectrical stimulat on of the rdiac elec t e nerves and also t exc se Now that lear evidence of l l benefit has bee recorded for ompound possessing true b k g properties propr nolol t ex tremel importa t that new ompound troduced t med al pract is equall well identified Recentl number of compound (previously ter lia, to possess β-receptor bl king properties. Should compound nat ural l alled β-blocker f l t produ the desired linical effect t ca only serv to bring that lass of agent int disrepute and thereby seriously h nder the progress of a genuinely new approach t ardiov sc lar disease

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REFERENCES

1. Br unwald E Ed Symposium on bet adrenergic recept r blockade Am J Cardiol 18:303 1966
2. Barger G and Dale, H H Chemical structure nd mpathommetic action of am nes, J Ph siol 41 19 1910.
3. Cannon, W B and Rosenblueth A A tonomic neur effector systems, New York, 1937 The Macmilla Compan
4. von Euler U S A pecific ympath mimetic ergone in adrenergic nerv fiber (ympathin) nd it relations t adrenaline and nor-adrenaline Acta physiol. Scandinav 12 73 1946.
5. Ahlquist, R P A study of the adrenotropic receptors, Am. J Phy iol. 153:586 1948.
6. Powell, C E., and Slater J H Blocking of inhibitory adrenergic receptors by a dichloro analogue of isoproterenol, J Pharmacol. & Exper Therap 122:223 1958.
7. Moran, N C and Perkins, M E. Adrenergic blockade of the mammalian heart by dichloro nalogue of isoproterenol, J Pharmacol & Exper Therap L.:223, 1958.
8. Black J W nd Stephenson, J S Pharmacology of new adrenergic bet recept r-blocking compound (Nethalide) Lancet 2 311 1962.
9. Black, J W Crowther A F Shank R. G Smith L. H nd Dornhorst, A C A new adrenergic beta-receptor tagonist, Lancet 1 1080 1964
10. M ra N C Aims of the conference Ann. New York Acad. Sc 139:545, 1967
11. Burns, J J Colville K I Lindsay L. A and Sal ador R A Blockade of some metabolic effect of catecholamines by N isopropyl me thoxamine (B W 61-43) J Pharmacol & Exper Therap 144 163 1964
12. Barrett A M The mobilization of free fatty acid in response to isoprenaline in the rat, Brit J Pharmacol. Chemother 25:545, 1965
13. Westerma n, E Drugs affecting the mobilization of f ee f tty acid Schettler and Sanald, editors Pathophy siological nd clinical pects of lipid metabolism Verlag Stuttgart, 1966 Georg Thieme p. 37
14. Levy, B and Ahlquist, R. P Blockade of the beta adrenergic receptors, J Pharmacol. & Exper Therap 130:334 1960
15. Blinks, J R Evaluation of the cardiac effects of several beta-adrenergic blocking agents, Ann. New York Acad. Sc. 139:673 1967
16. Fitzgerald J D nd Barrett, A M What is a β-blocker? Lancet 2:310, 1967
17. Grant R H E., M Devitt, D G. and Shanks, R C I erapamil a β-blocker? Lancet 1 362, 1968

Rapid determination of the area under indicator dilution curves

On-line analogue computers ar used for the electronic determination of the area under indic tor dilution curves. These machines are costly are subject to baseline drift, and require isual hecking t ensure that the curves are satisfactory Their major use is here rapid and frequent measu ement of cardiac output is necessary

A rapid mathematical method for anal sis of the area of an indicator d l tion curv has been described by Williams and associates. This method

```
         DIMENSION X (160, 25)
         DO 15 K    1, 160
         DO 15 L    1, 25
15       X(K, L)    0
         TWOY   4.0
         DO 11 K    1, 160
         SUBX   1.0
         DO 10 L    1, 25
         X(K, L)    SUBX  (2.0* TWOY / 3.0)
10       SUBX    SUBX    0.1
11       TWOY    TWOY    0.1
         DO 12 K    1, 160
         WRITE (3 2) (X(K, L) L    1, 25)
2        FORMAT (I3, 25 F5.1 / )
12       CONTINUE
         END
```

Fig 1

fits the curv ith three parabolas, rectangle, and an exponential. The formula used reads.

Area under curv =

$$\frac{2}{3}Y\ (X - X\ ) + Y\ [(X_4/3 + 10(X_4\ \ \ X_4)/7)]$$

The poi ts Y Y₂, X X₃, and X₄ are placed as described by Williams and associates and their alues can rapidly be obtained with a plastic T square or ruler. These authors ha show their method to be applicable to most of the indicator dilution curves usually obtained with the same limits of accuracy as any other method hen the cardiac output falls. I their series, ery close correlation exists between this nd other manual methods in common use.

I our laboratory the formula has been applied t series of curves and compared ith alues of the same curv obtained by planimetry after replotting on semilogarithmic paper. W also hav found very close correlation between these methods and now accept this formula as useful mathematical technique.

The formula is, however   little cumbersome even hen desk calculator nd mathematical paper are used. When numerous values are required immediately in the laboratory or t the bedside errors are made and   find it necessary to recheck the figures later using an IBM 360 computer for speed and accurac Unless some time-sharing device is llable in the laboratory for direct access to computer much time is still lost by a fully trained staff with delay in obtaining the final data.

T allow extremely rapid and accurate alues t be obta ned t the bedside, by semiskilled technicians, w ha e devised set of tables to determ ne sections of this formula, viz

$$A = \frac{2}{3}Y\ \ (X_3 - X\ )$$

$$B = Y\ \ (X_4/3)$$

$$C = Y\ \ (10(X_4 - X\ ) / 7)$$

Area under curve = A + B + C sq centimeters.

The set of tables may be generated using the programs shown, written in FORTRAN IV nd require total of 6 minutes computer time.

After the values of Y Y₂, X X and X₄ are obtained from the curves, it is necessary to determine (X − X) and (X₄ − X₄) and, using these values read directly the results of A, B and C from the tables. Computation of the area formula then becomes a matter of simple addition and needs no further checking. The mean time to obtain the area of each curv from beginning measurement is 90 seconds.

These programs are designed to generate a two-dimensional table. Values of X (X − X₁) nd (X₄ − X₂) from 1 to 8.4 cm in 0.1 cm. increment are on the horizontal axis and alues of Y and Y from 4 t 20 cm   0.1 cm. increments on the vertical axis.

Each table has only 25 of the 80 alues of X to allow each printout to be photocopied and put to booklet form.

The main program is show in Fig 1. The alue SUBX is altered to gi values 1.0 − 3.4 3.5 − 5.9 6.0 − 8.4 for X by setting is initial value at 1.0 3.5, and 6.0 respectively.

The arithmetic statement shown in Fig 1 is for A and this may be replaced ith

X(K, L) = TWO Y (SUBX/3)   for B
and X(K, L) = TWO Y (10 SUBX/7)   for C

The use of these tables allows ery rapid calculation of the area, and hence the cardiac output in the laboratory or t the bedside.

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REFERENCE

1 Williams, J L P O'Donovan, T P B and Wood, E H A method for the calculation of areas under indicator-dilution curves J Appl Physiol 21:695 1966

Letters to the Editor

Ischemic heart disease and diabetes mellitus

To the Editor:

Selvester and co-workers[1] recently reported that there were more irregularities in QRS vector loops recorded from patients with diabetes mellitus than from normal subjects and interpreted the results in relation to the known association between diabetes and coronary artery disease. Such observations may prove to be very useful in identifying myocardial abnormalities associated with coronary artery disease, but some of the more specific implications given to the findings deserve critical comment.

Selvester and co-workers used their results to define new criteria for diagnosis of myocardial infarction and reported the criteria to be present in 94 per cent of patients with maturity-onset diabetes, although standard electrocardiographic criteria were present in only 33 per cent. No clinical or pathological evidence was presented to confirm the diagnosis of myocardial infarction in any of the cases missed by standard vectorcardiographic criteria. Since healed myocardial infarction was found at autopsy in only 27 per cent of one large series of patients with diabetes[2] and 37 per cent of another series (none in patients under 30 years of age and 38 per cent in patients over 40 years),[3] it is likely that most of the patients identified by the new criteria without confirmatory electrocardiographic findings did not have lesions similar to those classified as myocardial infarction in the autopsy studies. Selvester and co-workers apparently prefer to broaden the definition of the term "myocardial infarction" so that it includes all myocardial abnormalities associated with coronary atherosclerosis, but since this results in two to three times as many diagnoses as were reported in autopsy studies of similar cases they certainly have an obligation to present a detailed description of the anatomical basis for their own definition of the term and a convincing rationale for its usage. It is also reasonable to require that when investigators propose new diagnostic criteria that apparently identify two to three times as many myocardial infarctions as were found in autopsy studies of similar cases, they should provide independent evidence confirming the presence of such lesions in their cases. The fact that the proposed new criteria were present in vectorcardiograms from 6 per cent of clinically normal subjects over the age of 2½ weeks and 12 per cent of a random sample of hospital employees over the age of 15 years further emphasizes the need for establishing the specificity of the criteria before considering them for general use.

Although there may be a logical basis for using the term "myocardial infarction" to encompass all types of lesions associated with coronary atherosclerosis, it must be realized that this classification would include a wide spectrum of differences in pathophysiologic, therapeutic, and prognostic factors. Ehrlich and Shinohara[4] recently reported striking differences in frequency of both coronary thrombosis and myocardial rupture in cases of acute myocardial infarction with circumscribed (unifocal) lesions as contrasted to cases with scattered foci of necrosis, and they suggested that it may be erroneous to apply the term "infarct," which refers to a more or less circumscribed area of tissue necrosis resulting from vascular insufficiency, to many of these lesions which possibly have resulted from as yet obscure mechanisms.

The harm that can be done by a diagnosis of serious myocardial disease based on an isolated nonspecific electrocardiographic finding has been emphasized by others[5-7] but may be overlooked when attempts are made to improve the sensitivity of diagnostic criteria without sufficient consideration for their specificity.

For the reasons mentioned above it seems logical at the present time to consider that irregularities of the QRS vector loop outside the range of normal represent unspecified myocardial abnormality unless additional and better-substantiated criteria for infarction are also present.

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REFERENCES

1. Selvester, R. H., Rubin, H. B., Hamlin, J. L., and Pote, W. W.: New quantitative vectorcardiographic criteria for the detection of unsuspected myocardial infarction in diabetics, Am. Heart J. 75:335, 1968.
2. Warren, S., Le Compte, P. M., and Legg, M. A.: The pathology of diabetes mellitus, ed. 4, Philadelphia, 1966, Lea & Febiger Publishers, p. 190.
3. Goldenberg, S., Morris, A., and Blumenthal, H. T.: Sequelae of arteriosclerosis of the aorta and coronary arteries. A statistical study of diabetes mellitus, Diabetes 7:98, 1958.
4. Ehrlich, J. C., and Shinohara, Y.: Low incidence of coronary thrombosis in myocardial infarction. A restudy by serial block technique, Arch. Path. 78:432, 1964.
5. Prinzmetal, M., et al.: Clinical implications of errors in electrocardiographic interpretation: heart disease of electrocardiographic origin, J. A. M. A. 161:138, 1956.
6. Marriott, H. J. L.: Electrocardiographogenic suicide and lesser crimes, Florida M. A. J. 50:440, 1963.
7. Langer, P. H.: Victims of the vector, Am. Heart J. 69:284, 1965.

Reply

T the Edito-

W have read Dr Borun letter with interest. However there are several points that need clarification.

I one example, percentage figures wer quoted that were from tudies not comparable to ou own. The use of the figures 27 nd 37 per cent, representing healed myocardial infarction found t autopsy in two series for whole diabetic populations (ncluding those with juvenile and maturity-onset diabetes), cannot be used in valid omparison to our figure of 94 per cent (8 per cent possible and 86 per cent definit infarct) f om those with maturity-onset diabetes only It is well known that the incidence of myocardial infarction in maturit onset diabetes is decidedly greater than in juvenile-onset diabetes. Therefore, the grouping of the two together reduces the total incidence of infarctions

The criterion for pathological diagnosis of healed infarct is defined in most series as circumscribed scars 2 cm. in diameter or larger This corresponds to the classification of large infarct by ou criteria. Instead of 94 per cent, mor comparable figure is the 33 per cent of our entire series who ere diag nosed as having such large lesions However these er living subjects and should still be lated with caution to the 27 t 37 per cent of healed infarcts in the pathological series referred to by Dr Borun.

W agree ith Dr Borun statement that the specificity of these criteria should be established before they are accepted for general use This as our intent in the summary when expressed the hope that this eport might stimulate number of adequately controlled pathological studies of suf ficient detail to erify whether these vectorcardiographic changes do indeed correlate with smaller scars in the myocardium. The fact that these changes or smaller scars are present in normal subjects is not surprising since linically silent infarcts do occur However the reference to the normal series hich led to the fort nate juxtaposition of 6 per cent abnormality to the age of 2 5 weeks or older is nother inappropriat manipulation of numbers Definit abnormalit was found in 3 per cent of ectorcardiograms and the ages of the subjects as reported in the article were 25 46 and 47 Again, the abnormalities in the random hospital population occurred in 11 per cent of subject and re ported were in the age group 25 to 37 (not 12 per cent of subjects over 15).

The question of appropriate nomenclature for smaller scars in the myocardium does seem to us to be reasonable one These scars are referred to by Woods and associates as schemic fibrosis and by Ehrlich and Shinohara[2] as multifocal infarcts. I the patients with mat rity onset diabetes of the present series, the 86 per cent definite infarcts almost certainly represent scar in the m ocardium secondary to coronary artery disease. Drs. LeCompte and Legg, in personal communication, note that coronary occlusion nd myocardial infarcts of arious ages accounted for 42 3 per cent of the deaths in our utops series of 1 036 diabetic pa tients from 1948 through 1963 It seems quit possible that the umber of patients with small myocardial scars would increase the percentage significantly but specific careful studies to find small myocardial scar has not been done as far as we know in the type of diabetic population that Dr Sel ester has studied. The changes that we call diffuse fibrosis in ou report has been observed by us in large number of patients with rheumatic heart disease and certainly are nonspecific. F rther more the recent flurry of eports of linical infarc tion, including classical lectrocardiographic and ectorcardiogr phic changes of infarction in patients th normal coronary arteries, do suggest the need t re-examine terminology That is why w used the term fibrosis and/or infarction in our report. Perhaps it would be mor scientifically correct if the smaller but definitely abnormal changes on vectorcardiographic loops ere termed consistent with m ocardial fibrosis (small or medium-sized area), and that more classical changes called more succinctl large infarct in our paper were termed consistent with a large area of myocardial fibrosis and/or infarction.

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REFERENCES

1 Woods, J D Laurie, W and Smith, W G The reliability of the lectrocardiogram in myocardial infarction, Lancet 2:265 1963
2 Ehrlich, J C and Shinohara, Y Low incidence of coronary thrombosis in myocardial infarction A restudy of serial block technique, Arch. P th. 78:432 1964

New quantitative vectorcardiographic criteria

T the Editor

Recently Selvester nd co- orker published report entitled New qua titative vectorcardiog phic criteria for the detection of unsuspected myocardial infarction in diabetics. The difficulties in recognizing infarcts in diabetics, ha been widely recognized nd every ttempt needs t be made to refine tech iques for this diagnostic problem. The author are proposing new criteria which could eventually lead t considerable improvement in inf rct recognition They are based mainly on arcilike deformities of QRS loops which have been described first in cases of myocardial infarct by Burch and co-workers T some extent, they correspond to the notches and slurs described by Langner and associates[4] in scalar lead It is commonly assumed that such notches, dents or arcs are due to a fragmentation of entricular activation fronts, and Durrer and olleagues[5] have given substantial evidence for this assumption

The interpretation of such QRS deformities poses several problem (1) Are they necessarily reflection of m ocardial lesions or ar some of them (particularl those of short dur tion) only a normal variant of QRS configuration? (2) I there a one to-

one relationship between QRS deformity and the size of a myocardial lesion postulated by Selvester. (3) What are the best recording and display methods for analyzing QRS deformities.

Normal limits for deformities. QRS loops were described several years ago, based on 249 recordings on patients between the ages of 20 and 73. QRS loops were analyzed in broadside projections because small deviations from this projection plane which are normal may appear as deformities in other projections. Up to 2 QRS dents of 5 msec. in duration or more were found in as many as 55 per cent of this normal population. The mean duration was 12 ± 5 msec. Using the criteria of Selvester, the majority of these normal subjects would have been judged to have infarcts. It may be argued whether all normal subjects were really free of coronary artery disease, particularly those in the older age groups. This represents a definite limitation of all studies on normals, but it appears unrealistic to assume frank infarcts in more than half of a population without history of chest pain and/or other signs and symptoms of heart disease. The conclusion drawn from our data has been that up to 2 QRS deformities, of less than 22 msec. in duration, should be considered as normal variants. Those of longer duration corresponding to the area of Burch and co-workers can be safely considered as abnormal. Most of the notches described by Langner and co-workers[3] can also be identified in vector loops. These authors considered up to 10 notches in a single lead or up to four in a combination of three selected leads as normal.

At this point one can only speculate about the causes of QRS deformities in normal subjects. Reversals in activation front orientation when the epicardial surface is reached and other directions suddenly dominate may be one cause. In many cases they are probably due to small fibrotic lesions as indicated by their increased frequency not only in coronary artery disease but also in ventricular hypertrophies. When such small lesions involve terminal branches of the Purkinje system, their effect may be accentuated. It is only reasonable to expect an increased frequency of small QRS dents in diabetic microangiopathy, but to label all such microscopic lesions as "infarcts" in the usual sense would be difficult to justify. Using the criteria of Selvester may lead to an intolerable number of cases with "heart disease of vectorcardiographic origin."

To relate the size of a QRS deformity to the size of an "infarct" appears highly speculative. This relationship is very tenuous at best, as indicated by the frequent finding of large infarcts with relatively small QRS changes and small lesions with very pronounced ECG alterations. Much more research is needed to elucidate this problem. The fact that dentlike QRS deformities can be simulated by an analogue, which is quoted by Selvester as evidence for the presence of infarcts, is difficult to accept because any ECG change can be simulated. It will by practically an infinite variety of analogue settings.

As to the best methods for displaying QRS deformities, the overriding importance of the proper amplifier frequency response needs to be stressed. Although the oscilloscope has no limitation for this characteristic, it is unfortunately common practice to use amplifier high-frequency cutoffs of 100 Hz or less in order to obtain clean tracings. To double gain and paper speed for direct writers in order to display fast QRS notches, as recommended by Selvester, is of very limited value when the frequency response of the instrument is not higher than 50 Hz. Practically all direct writers in present use do not exceed this limit. They have been extended to 100 Hz. only recently in the new AHA *Recommendations on ECG Instrumentation*. Even this limit is inadequate for recording of high frequency components and the recommendations for VCG recording should be followed. Unless a uniformity in recording is achieved, every vectorcardiographer could conceivably establish normal limits for QRS deformities of his own reflecting only the poor characteristics of his recording system.

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REFERENCES

1. Selvester, R. H., Rubin, H. B., Hamlin, J. A., and Pote, W. W.: New quantitative vectorcardiographic criteria for the detection of unsuspected myocardial infarction in diabetics, Am. Heart J. 75:335, 1968.
2. Burch, G. E., Horan, L., Abildskov, J. A., and Cronvich, J. A.: A study of the spatial vectorcardiogram in subjects with posterior myocardial infarction, Circulation 12:418, 1955.
3. Langner, P. H., Geselowitz, D. B., and Mansure, F. T.: High-frequency components in the electrocardiogram of normal subjects and patients with coronary artery disease, Am. Heart J. 62:746, 1961.
4. Durrer, D., Formijne, P., van Dam, R. T., Buller, J., van Lier, A. A. W., and Meyler, F. L.: The electrocardiogram in normal and some abnormal conditions in revived human fetal heart and in acute and chronic coronary occlusion, Am. Heart J. 61:303, 1961.
5. Pipberger, H. V., and Carter, T. N.: Analysis of the normal and abnormal vectorcardiogram in its own reference frame, Circulation 25:827, 1962.
6. Kossmann, C. E., Brody, D. A., Burch, G. E., Hecht, H. H., Johnston, F. D., Kay, C., Lepeschkin, E., Pipberger, H. V., and Members of the Subcommittee on Instrumentation: Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Report of Committee on Electrocardiography, American Heart Association, Circulation 35:583, 1967.

Reply

To the Editor:

Dr. Pipberger's comments will be discussed in the three main areas: (1) the normal range of variability

for QRS deformities (2) the relationship of the size of myocardial scar to the size of the QRS deformity and (3) recording and display methods.

First, in evaluating the normal range of variability of QRS deformities, the method proposed by Dr Pipberger of drawing tangent across a concavity or dent in a "broadside" projection of a vector loop is similar to our method but with important exceptions.

1. The tracings in the series reported by Pipberger were from vectors taken partly with the SVEC III and partly with the Frank lead system. Our tracings were taken with the Cube lead system. We have recorded 300 VCGs simultaneously with four lead systems (SVEC III Frank McFee and Cube) over the past 3½ years, and routinely all corrected lead systems with averaging networks contain considerably less high-frequency notching than does the uncorrected Cube lead system. These are quite different from large smooth concavities or dents on the loop described by Pipberger as occurring in normals. When we applied Pipberger' method to our normal series recorded with the Cube system we found 35 per cent with these concavities on the loop.

2. In Pipberger' method, there is no account taken of the magnitude of the concave or dent displacement. Small concavities by this method are common in our normal series but usually less the 0 7 mv and always smoothly written—that is, there is no additional high-frequency notching in the concavity and the dots are transcribed smoothly with regular spacing between them. These were considered as a smooth loop by us in establishing the criteria proposed for small and medium-sized areas of fibrosis and/or infarction.

3 Pipberger' method looks only at concavities or dents in an ovoid loop An outward-bowing high-frequency convexity or "bump" in a "broadside" projection, when tangential lines are drawn to smooth out the deformities, would result in two dents being recorded. The duration would be dependent on the magnitude of the original deformity but could result in two dents of 15 to 20 msec. each. Our criteria consider displacement either outward or inward from a smooth loop as similar abnormalities. The direction of the displacement will be dependent on where on the three-dimensional double cone of activation the loss of generators occurs.

4 Pipberger' normals were taken from V. A. hospital patient population and their average age (40) is older than that of our patients (20). His series will probably contain higher number of patients with unsuspected areas of infarction 2 cm. or larger. This figure approached 6 per cent in one large hospital series

5 Criteria developed from a "broadside" projection of rotated loop ignore changes normal to the plane of the loop, and high-frequency changes of large magnitude can occur in this direction and not be accounted for

The second major question raised by Dr Pipberger has to do with the relationship of the size of the myocardial lesion to the size of the QRS deformity on the vector loop. He properly doubts a one-to-one relationship. Our model is built from anatomical and physiological information about the activation front and, as such, is one of an infinite number of possible generator configurations that can account for the surface VCG Because it does contain important anatomical and physiological constraints, however it is a unique generator that can clearly be analogized to a real heart. Simulation of hypertrophy of either ventricle, right and left bundle conduction defects and large infarcts in all the classical locations are indistinguishable from those observed in clinical vectorcardiography and as such help validate the model. It is therefore quite reasonable to analogize to smaller lesions. What is now needed, as we argue in the paper is careful correlation of these vectorcardiographic changes with complete pathological maps of the myocardium at autopsy Since the criteria generate predictions of lesions 5 mm or larger in size clearly the pathological examination must include the whole heart by serial sections at this 5 mm interval or less Simulated multiple large infarcts on opposite sides of the heart like those observed in clinical cardiology often neutralize each other either partially or totally This confounding always produces an underestimate in the size of the infarct In no instance in the simulations did the proposed criteria when applied to simulated multiple infarcts overestimate the size of the infarct. We feel, therefore, that the proposed criteria, while crude at best, are conservative and do give a reasonable estimate of the size of the area of destroyed myocardium where single lesions are present The degree to which this hypothesis is valid can be verified only by careful pathological study as outlined above

Third, the comment by Dr Pipberger about amplifier and recorder are highly important considerations The amplifier used for the vectorcardiograms in our study had a high frequency cutoff at 1500 Hz We have been using double gain, double speed on our direct written electrocardiograms for 3½ years and even with the poor characteristics noted by Dr Pipberger we have seen routine notching on P waves at this gain (similar to those recorded by Brody) that are usually not seen on standard ECGs. We have also seen much clearer depiction of the multiple notching in QRS in patients with coronary disease. It is clear from our data that, in spite of the limitations of the recorder when these records are taken at twice the usual speed and gain, significant additional information is obtained.

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REFERENCE

1 Johnson, W J Achor R W P Burchell, H B and Edwards, J E. Unrecognized myocardial infarction, Arch Int. Med. 103:253 1959

Book reviews

The Epidemiology of Hypertension. Edited by Dr Jeremiah Stamler, Mrs. Rose Stamler and Dr Theodore N. Pullman, 1967. Grune & Stratton Inc 472 pages. Price $17.50

This 480 page volume is an account of the proceedings of an International Symposium held in February 1964 on the Epidemiology of Hypertension. It follows the format of reprinting the papers presented plus an abridged version of the discussion that followed each paper. In all some 34 papers are represented. They are grouped logically each under the heading of the specific factor thought according to current thinking among the experts to influence hypertension. Examples of the headings under which the papers are grouped are Genetic, Age, Sex, Body Habitus, Family, Race and Nationality, Environmental Factors such as Diet, Salt, Smoking and Alcohol, Environment, Socioeconomic Factors, etc.

For those of us that follow the literature on this subject the material covered in this conference is surprisingly current, despite the 3 years that have elapsed since its presentation. It touches on all the major areas of investigation in hypertension epidemiology and brings out clearly the various areas of doubt and controversy (such as, for example the genetic versus environmental debate). While it is not primarily a book for practitioners, there is no question that the practitioner who wishes to understand some of the factors that may well be influencing his group of hypertensive patients can benefit greatly from it, both in terms of his own understanding of hypertension and in terms of the advice he will give his patient. The groups to whom it is specifically geared are epidemiologists, and especially epidemiologists in the cardiovascular field. Its real value for this group is the pulling together into a single text a current summary of the directions and concepts in the epidemiology of hypertension.

The editing deserves a special note of praise. If indeed such a book can be made readable and enjoyable through the editing technique this has been done effectively by Dr Stamler and co-editors.

In summary the book is of a special value to epidemiologists in the cardiovascular and hypertension field but will be read with profit by internists and general practitioners who wish to enhance their own understanding of hypertension and the factors that affect it, and to pass on to their patients some of this information.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. 33 Tagung. Edited by R. Thauer and C. Albers, Darmstadt, 1967. Dr D Steinkopff Verlag, 286 pages.

The main topic for the 33rd Annual Meeting of the Deutsche Gesellschaft für Kreislaufforschung (March 31 to April 2 1967) was circulation and kidney. Of the 42 articles in the volume, 21 are concerned with this topic (pages 1 to 160). The opening address of H. Schwiegk is largely tribute to the memory of Bruno Kisch who died Aug 12 1967. He founded in 1927 with A. Weber the Gesellschaft fur Kreislaufforschung and later with F. Groedel the American College of Cardiology.

As in all previous meetings, there was an international flavor with invited speakers from the United States (W. J. Kolff), Switzerland (A. F. Müller) and France (F. Zacouto).

The coverage of the complex relationships between circulation and kidney (normal regulations cardiac and kidney diseases hypertension) is comprehensive. There is a wealth of up-to-date information, much of it not previously published.

It is, of course not possible to review 42 articles in this limited space. Therefore, a few arbitrary selections may suffice to give a general impression of the content. K. Thurau (pages 1 to 15) presents a review of kidney circulation, correlated to kidney functions, followed by A. F. Muller and R. Veyrat's review of kidney and blood pressure regulation (pages 16 to 29). It is concluded that the dynamics of the renin-angiotensin system with its activators and inhibitors, except the phospholipid fraction described by Bumpus is still largely unknown, and that the relationship between renin and blood pressure is quite complex. The role of the kidney in the regulation of blood volume is discussed by Y. Reecker (pages 30 to 47), with a diagram illustrating the intricate feedback mechanism.

Two reviews are concerned with the effect of cardiovascular disorders on kidney function (E. Buchborn Circulatory shock, pages 47 to 59 E. Wetzels Cardiac surgery pages 59 to 70). Wetzels survey of 2 000 cases with cardiac surgery is subdivided into type of defect and surgery (with or without hypothermia) incidence of kidney failure, and mortality. The actual problem of kidney transplants and artificial kidney is presented by W. J. Kolff (pages 70 to 72). H. Edel and Pichlmaier (pages 116 to 119) investigated the effect of the time lapse from the moment of the donor's death to transplantation, with kidney kept "warm" (i.e. without cooling) or cooled to 4° C. with transfusion. The critical time for kidney kept "warm" is 70 minutes. G. Heberer (pages 73 to 83), reviewing his material of renal surgery of nephrogenic hypertension, with follow-up of 7 years, concludes that in patients under 40 years with renal artery stenosis the results of renal surgery are so favorable that it is indicated in most cases.

W. J. Kolff (pages 211 to 213) reports briefly about animal experiments with an artificial heart inside the chest (pages 211 to 213), followed by F. Zacouto's paper on his experience

with an implanted artificial (auxiliary) ventricle in experiments in dogs. L. Renggli and associates (pages 182 to 185) compared resting electrocardiogram (ECG), exercise ECG, and incidence of angina pectoris in 2,875 employees of pharmaceutical companies in Basel (Switzerland). Thirty-t per cent had an abnormal resting or exercise ECG exceeding the prevalence of other similar samples. However only 10 per cent of those with abnormal ECG had clinical coronary insufficiency. Unfortunately they used as criterion for an abnormal exercise test the QX/QT ratio of ≥ 50 per cent which has been shown to be worthless by several investigators, and the same criteria for S-T depression in the exercise and postexercise ECG which is bound to exaggerate the percentage of abnormal tests.

The volume is profusely illustrated, and the cardiologist will find much valuable information for his general or specific interests.

TREATMENT OF HEART DISEASE IN THE ADULT. By Ira Lloyd Rubin, M.D., Harry Gross, M.D., and Sidney R. Arbert, M.D. Philadelphia, 1968, Lea & Febiger Publisher. 393 pages. Price $17.50.

The material in this book is presented in a more or less outline fashion. The discussions are clear and the opinions and practices of the authors are concisely described. They discuss heart disease due to coronary disease, hypertension, congenital defects, pulmonary diseases, bacterial infections of the endocardium and pregnancy as well as other causes. Digitalis, diuretics, intensive care units, surgery and rehabilitation are briefly but clearly presented. This is ery good book because of its brevity, clarity and usefulness to busy physicians as well as residents and interns. The authors have adhered to the conventional practices of good cardiology. Some cardiologists will have different views but few if any ill be important.

RESUSCITATION—A PROGRAMMED COURSE. By Leonard P. Caccamo, M.D., Edward Kessler, M.D., and J. Leonard Ameer, Ph.D. Philadelphia, Pennsylvania, 1968, F. A. Davis Company. 113 pages. Price $2.50.

This is another brief and simple manual on cardiac resuscitation. The text is brief and the illustrations numerous and simple. The manual is accurate and good for beginners, especially nurses and laymen.

MYOCARDIAL INFARCTION. Proceedings of the 9th Conference of the International Society of Geographical Pathology. Basel, Switzerland, 1967, S. Karger. 427 pages. Price $19.00.

This is the Proceedings of the 9th Conference of the International Society of Geographical Pathology held in Leiden, Sept. 8 through 10, 1966. The sessions were concerned with 3 problem of myocardial infarction viz. myocardial infarction inquiry, biochemistry and pathology and epidemiology. Forty-eight papers were presented, each well illustrated, clearly and concisely written and appended with bibliography. The pathology and incidence of coronary artery disease and myocardial infarction for several widely separated areas of the world were described. Although the incidence tended to vary in an already known manner the pathology was essentially the same. Although the various authors described their finding and opinions concerning the important disease the reader is impressed by the lack of really new idea or approach to the pathogenesis of arteriosclerosis and myocardial infarction. However this is a good book.

MÉCANIQUE DU COEUR ET DES ARTÈRES. Par L. Vadot, Paris, 1967, L'Expansion Scientifique Française. 254 pages.

Doctor Vadot has written brief discussion on the mechanical aspects of the physiology of the heart and blood vessels. The presentation is clear and the illustrations appropriate. H employs effectively the theories of electronic circuits to support his thoughts, a good practice used in many laboratories concerned with hemodynamic theoretic discussions. His bibliograph is brief. However the historical developments of many of the concepts are not accurate. Unfortunately like many other writers today the literature is not carefully and thoroughly reviewed. These failures are reflected in the lack of thoroughness of some presentations. This is a interesting and useful book.

ARBEITSMETHODEN DER INNEREN MEDIZIN und ihr verwandter Gebiete. By Professor Dr. med. Rolf Emmrich Jena, 1967 Leipzig, Veb Gustav Fischer Verlag. 208 pages.

This volume is concerned with 2 methods used in internal medicine for the study of the patient with heart disease. The first part described cardiac catheterization and the second electrocardiography and vectorcardiography. The first method is presented very well and should be useful to the beginner. In spite of the rapid changes in equipment and electronics, readers will still find the discussion of conventional curves and their analyses most rewarding. The illustrations and discussions are very good. The second section devoted to electrocardiography and vectorcardiography is extremely thorough. It represents an excellent brief review of the subject. Although all methods, publications and points of view are not discussed, those presented give the reader a very good insight into the problem of the fields. The only reservation one can find is lack of a critical discussion of the practical clinical aspects of vectorcardiography. This is useful book.

Announcement

TRAVEL GRANTS The American Academy of Allergy will again ward tra el grants for its Twenty-fifth Annual Meeting in Bal Harbour Fla., March 15 t 19 1969 Supported in part by the Schering Corporation these gra t w'll be warded on the basis of merit. Candidates mu t be sponsored by a Fellow of the Academy and should be in full-time llergy and immunology training Application forms may be obtained from the Executive Office, 756 North Milwaukee St., Milwaukee Wis. 53202 The deadline date for submission of applications is Jan. 10 1969

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Editorial

Cardiac causalgia

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Pain in the chest frequently offers considerable difficulty in diagnosis and treatment. The pain of heart disease is no exception. When the pain of ischemic heart disease is classical Heberden type, any clinician can easily recognize the cardiac origin. Fortunately the pain is classical in most instances. Nevertheless, in some patients it is still often difficult and confusing to interpret. Many of these patients are elderly so that hiatal hernia, radiculitis, arthritis, bursitis, cholelithiasis, diverticulitis, and other states well known to produce pain in and near the chest can make diagnosis extremely difficult even for the most astute cardiologist. That accurate diagnosis is essential for successful therapy requires no further comment.

For the past 25 or more years, we have been impressed with one type of chest pain syndrome which has offered considerable difficulty not only in diagnosis and treatment but also in interpretation as to pathogenesis. This chronic and almost intractable pain develops in association with heart disease, usually ischemic heart disease, and in postthoracotomy states.

Typically the patient has had a myocardial infarct or advanced myocardial ischemia with angina pectoris. The infarct may be fairly recent or it may be old, in which case it is usually followed by severe angina pectoris. In rare instances there has been angina pectoris without clinically recognizable myocardial infarction. Frequently the cardiac disease has been improperly treated and the usually effective measures in medical management have been neglected. Some patients in recent years have been subjected to revascularization surgery with the syndrome developing or worsening after operation.

In addition to the true heart pain of angina pectoris which among other classical features is characteristically precipitated by exertion, emotional disturbances, and eating, and relieved by rest and nitroglycerin, the patient has another syndrome associated with chest pain of a different type. The pain of this latter syndrome is severe, often burning in character, and found anywhere in the chest, but is usually most pronounced anteriorly on the left side. It is of long duration, lasting several hours to days or even months. It can be excruciating and is usually not related to exertion or emotional disturbances. Paresthesias are frequently present. The discomfort is relieved very little if at all by nitroglycerin, and is most severe at night or when the patient is alone and not dis-

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tracted. The fact that the pain of angina pectoris is relieved by nitroglycerin whereas the pain of cardiac causalgia is not makes nitroglycerin a useful drug in diagnosis and differentiation of the two types of pain by both the patient and the physician. There are frequently numerous tender trigger points in the chest wall which when pressed upon can precipitate or aggravate various aspects of the pain. There may be associated muscle, fascial, arthritic, and bursal tenderness along with pain and restriction of movement of usually the left arm, shoulder, chest, back, and neck because of exaggeration of the pain. The skin of the arm and shoulder may appear slightly shiny and manifest some dystrophy. This pain syndrome has all of the characteristics of causalgia minor or major[1-4] so well known in the arm or leg in the field of peripheral vascular diseases.

Thus, cardiac causalgia has the pain characteristics of neuralgia or sympathalgia. The spectrum of intensity and incapacity produced in the patient is wide. The syndrome varies from mild discomfort with little impairment of the patient's function to intense pain and complete incapacity. Unless great caution is exercised, as in any type of causalgia, opiates are used in excess and addiction follows.

Patients with cardiac causalgia are extremely difficult to manage. As with causalgia originating in the limbs, the pain can be intense, and the usual therapeutic measures such as rest, physical therapy, and analgesics are of no avail. The patient eventually seeks advice from one doctor after another, tries any form of therapy, and is often labelled "neurotic," "psychotic," "hysterical," or "psychopathic." Nevertheless, as with the well-known forms of causalgia or neuralgia, the patients have genuine pain and should be treated accordingly.

As with the well-known forms of causalgia of the limbs, this syndrome of cardiac causalgia is pathogenetically poorly understood. It is not inconceivable that visceral causalgia can exist as well as peripheral or extremital causalgia. Myocardial ischemia, especially with infarction or cardiac injury following physical trauma as with surgery, could conceivably initiate the syndrome just as injury to an artery and/or nerve of a limb by direct physical trauma produces extremital causalgia. The heart is a specialized segment of the arterial system. It is richly innervated by the autonomic nervous system and has pain fibers. Thus physical injury to the heart might well be expected to result in a causalgia-like syndrome.

It is likely that the postmyocardial infarction syndrome, the shoulder-hand syndrome, and the postthoracotomy syndrome are variants of the same causalgic state. When recognized early and treated promptly and properly, the causalgic state responds with complete relief. However, if neglected in the early stages, the classical chronic mild-to-severe causalgia syndrome follows and the patient obtains little or no relief regardless of when and what treatment is instituted. Cardiac causalgia can be prolonged or even everlasting in its course, fluctuating only in intensity. Unless recognized by the physician and carefully explained to the patient, it can be confusing to all involved.

As with causalgia major of a limb, cardiac causalgia can be associated with the accumulation of edema fluid of varying amounts. Cardiac causalgia can be associated with interstitial edema of the lungs, pneumonitis, pericarditis, and/or pleuritis with or without effusion, periarticulitis, and arthritis of the left and occasionally both shoulder joints, elbows, wrists, and hands. Edema of the left upper extremity is most common but bilateral edema may occur on rare occasions. The pulmonary and pericardial involvement in the so-called postinfarction and postthoracotomy syndromes are well known to be associated with diffuse, often severe pain with trigger points and tender spots of the chest wall.

The close relationship of the pain syndrome associated with heart injury to the pain syndrome of causalgia of a limb has prompted us to consider them the same pathophysiologic state, the only difference being their anatomic location. The pathogenesis, clinical manifestations, prognosis, management, and prevention of the two causalgic syndromes are all essentially the same.

Cardiac causalgia needs recognition in the clinic and proper management. Even

the best management can be most disappointing and discouraging to all, especially to the invalid patient. The pathogenesis of causalgia has received little attention It can be a crippling and pathetic disease.

REFERENCES

1. Burch, G. E. and Phillips, J. H.: Peripheral vascular diseases: diseases other than atherosclerosis, in Handbook of physiology vol. 2, Circulation, Washington, D. C., 1963 American Physiological Society pp. 1215-49
2. Hobler L. L.: Causalgia and causalgic states, Indust. Med. 12:724 1943.
3. DeTakats, Geza Nature of painful vasodilatation in causalgic states, Arch. Neurol. Psychiat. 50:318, 1943
4. Lewis, T.: Vascular disorders of the limbs ed. 2, London, 1949 The Macmillan Co.
5. Doupe, J Cullen, C., and Chance, C. Post traumatic pain and causalgia syndrome, J Neurol. Neurosurg Psychiat. 7:33, 1944.

Clinical communications

Combined aortic and mitral incompetence: Clinical features and surgical management

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The purpose of this report is to analyze the problem of mitral incompetence in 39 patients with aortic insufficiency as a coexistent major valvular lesion. The clinical and hemodynamic features are described and results of surgery are discussed. Attention is particularly called to the association of aortic insufficiency with ruptured mitral chordae tendineae.

Patient material

The records of all patients with a diagnosis of combined mitral and aortic incompetence established at cardiac catheterization from March 1948 through December 1966 were reviewed. The diagnosis was usually based on supravalvular aortic and/or left ventricular angiographic studies combined with analysis of the "V" waves in the left atrial or pulmonary wedge pressure tracings. Thirty-one patients were found with this combination of lesions in whom the diagnosis was later confirmed either at open heart surgery or autopsy examination. Six additional patients were included with strong clinical evidence of combined aortic and mitral regurgitation who underwent confirmatory cardiac surgery without a preliminary catheterization study. Two patients with autopsy proven ruptured chordae tendineae complicating aortic incompetence were also included. In all cases, the diagnosis was confirmed either at open heart surgery or autopsy examination. Patients were included only if incompetence appeared to be the predominant aortic and mitral valvular lesions.

Results

The 39 patients were divided into 3 groups on the basis of the cause of the

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mitral incompetence. These groups were as follows

Group I (12 patients) aortic insufficiency with rupture of the mitral chordae tendineae *Group II* (13 patients) aortic insufficiency with functional mitral insufficiency as a consequence of left ventricular failure. In all 13 cases, regurgitation through a normal mitral valve was found at cardiac surgery and clinical signs of mitral regurgitation disappeared after aortic valve replacement and *Group III* (14 patients) aortic insufficiency with mitral regurgitation due to organic rheumatic mitral disease. In 3 patients, mitral incompetence was primarily the result of prior mitral valvulotomy

The aortic incompetence was of rheumatic etiology except for one patient with luetic aortic insufficiency in Group I another with rheumatoid spondylitis in Group II and a third patient in Group II with a paraprosthetic aortic valvular leak. One patient in Group I had Ehlers-Danlos syndrome.

Clinical features

Pertinent historical and biographical data are shown in Table I

Age and sex. The average ages at time of study were similar in all groups. Men predominated over women in both Groups I and II with a striking predominance in the latter In contrast, women slightly outnumbered men in Group III

Previous history of rheumatic fever or bacterial endocarditis Previous rheumatic fever was most common in Group III while bacterial endocarditis was particularly common in Group I

Clinical course and symptoms The age of onset of first symptoms was similar for the 3 groups but progression of symptoms was considerably more rapid in Groups I

Table I *Biographical and historical features in the 39 patients*

Group	No. of patients: Male	No. of patients: Female	Prev R.F	Prev S.B.E.	Age first symptoms (yr)	Age at cath. or op (yr)	CHF	Years onset of CHF to cath or op	Syncope	Angina	Systemic emboli
I	7	5	6	5	38.4	43.3	11	1.2	1	3	0
II	11	2	7	3	42.3	44.5	10	2.5	1	7	0
III	6	8	13	1	41	46.5	14	5	1	1	2

R.F. Rheumatic fever S.B.E., subacute bacterial endocarditis, and CHF congestive heart failure.

Table II *Physical findings in 39 patients (murmurs graded 0 to 6+)*

Group	Water hammer pulses	Aortic murmurs: Diastolic 1+ to 2+	Aortic murmurs: Diastolic 3+ to 4+	Aortic murmurs: Systolic 1+ to 2+	Aortic murmurs: Systolic 3+ to 5+	Mitral: Systolic 1+ to 2+	Mitral: Systolic 3+ to 4+	Mitral: Diastolic Rumble	Apical S gallop	O S
I (12)	6	6	6	9	2*	2	9*	8	7	1
II (13)	8	4	9	4	9	4	6	9	8	0
III (14)	1	8	5	7	7	5	9	12	8	3

*Intensity not stated in some cases.

and II than in Group III Rapid deterioration was particularly marked in the group with ruptured chordae 8 of whom required surgery within a year after the onset of symptoms of congestive failure

Congestive heart failure was a major problem in 35 of the 39 patients. It was the cause of the presenting symptoms in almost all of the patients in Groups I and III but in only half of the patients in Group II

Angina pectoris was most common in Group II including 4 patients in whom it was the presenting symptom Syncope was unusual in all groups, and systemic emboli occurred only in Group III

Physical findings Table II records some of the pertinent physical findings. Peripheral manifestations of severe aortic regurgitation were observed in 6 patients in Group I 8 in Group II and only 1 in Group III Unsuspected severe silent aortic regurgitation was discovered at surgery in one patient from Group III The aortic diastolic murmurs were generally softer in Group III

Loud apical pansystolic murmurs, often with a diastolic rumble were heard in all cases. In one patient from Group I and 2 from Group II the apical pansystolic murmur was considered unusually harsh Appearance of this murmur under observation was documented in one patient from Group I and a sudden increase in intensity was noted in another In both instances, the change was in association with an episode of bacterial endocarditis. Palpable thrills were rare. Atrial gallops were not noted on auscultation

Six patients, including 2 from Group I and 4 from Group III had murmurs characteristic of tricuspid insufficiency

Abnormalities of the first sound were largely confined to Group III in whom increased intensity was noted in half Decreased intensity of the first sound was specifically noted twice in Group II

The intensity of the pulmonic closure sound was commonly increased in Groups I and III but this was unusual in Group II Decrease in the intensity of aortic closure was noted occasionally in all groups.

Electrocardiographic features

Atrial fibrillation occurred in all but one patient in Group III whereas it appeared only 4 times in Group I and twice in Group II Left ventricular hypertrophy was the

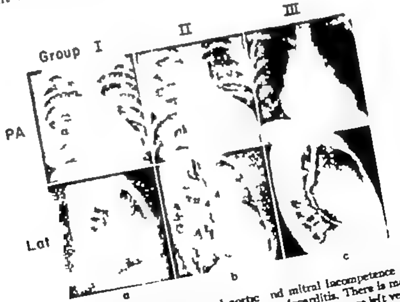

Fig 1 Representative radiologic findings in combined aortic and mitral incompetence *Group I* aortic incompetence with ruptured mitral chordae tendineae following endocarditis. There is moderate enlargement of left ventricle and left atrium with pulmonary congestion *b Group II* very large left ventricle seen in severe aortic incompetence with left ventricular failure. The left atrium is only slightly enlarged; and *c Group III* rheumatic mitral and aortic incompetence. Left atrial enlargement is quite marked with less striking increase in left ventricular contour

predominant QRS abnormality being present in 12 patients in Group I 9 in Group II and 10 in Group III Right ventricular hypertrophy was seen only once each in Groups I and III Two patients in Group II had left bundle branch block and 3 in each of Groups I and II had first degree block. Electrocardiographic signs of left atrial enlargement were rare.

Radiologic findings

X-rays were available for interpretation in 29 patients, and were reviewed without knowledge of the patient's diagnosis. Left ventricular enlargement was present in all groups, but the greatest enlargement was seen in Group II (Fig 1,b) and the least enlargement in Group III (Fig 1,c) Mild to moderate enlargement of the left atrium was seen in Groups I and II (Figs. 1,a and 1,b) while marked enlargement was characteristic of Group III Nine of 11 patients in Group III showed left atrial enlargement, which was judged to be disproportionately greater than the degree of concomitant left ventricular enlargement (Fig. 1,c) This combination was rarely seen in the 2 other groups. Right ventricular enlargement was noted in all groups, but right atrial enlargement was uncommon except in Group III Calcification of the aortic valve was seen in 9 patients from Group II and 4 from Group III but in none from Group I. Mitral valve calcification was observed in 10 patients from Group III one in Group I and in none of Group II

Catheterization and angiographic findings

Cardiac catheterization findings were available for 31 patients. Pertinent information is shown in Table III The data recorded is that obtained at rest.

The average height of pulmonary wedge or left atrial "V" waves was highest in Group I but this was not a statistically significant difference. However giant "V" waves measuring 30 mm. or greater were present in 4 of 6 patients in Group I 3 of 11 in Group II and only 2 of 14 in Group III Mean pulmonary artery pressures were highest in Groups I and III

Right ventricular failure was common in all groups. Elevation of pulmonary arteriolar resistance occurred most commonly in Group III Left ventricular end-diastolic pressures averaged 18 mm Hg in Groups I and II compared to 10 mm. Hg in Group III a statistically significant difference. The average cardiac index was reduced to a similar degree in all groups. Mitral end-diastolic gradients were seen in 4 patients from Group I 2 patients in Group II and in 10 patients in Group III

When angiographic studies were done, severe aortic regurgitation was most frequent in Groups I and II and severe mitral regurgitation in Group III

Table III Catheterization results in 31 patients

Group	"V" wave (mm Hg)	PC (mean) (mm Hg) (0 to 12)	PA (mean) (mm Hg) (10 to 20)	RVED (mm. Hg) (−5 to +5)	LVED (mm Hg) (0 to 12)	MEDG (mm. Hg) (0)	C.I (L/min/M²) (2.5 to 4.0)	PAR (units) (0 to 4)
I (6)	29	21	36	6	18	11	2.2	2.9
II (11)*	23	21	28	7	20	2†	2.2	2.7
III (14)	24	23	40	7	10†	10	2.3	5†

Abbreviations: PC, pulmonary capillary wedge pressure; PA, pulmonary artery pressure; RVED, right ventricular end-diastolic pressure; LVED, left ventricular end-diastolic pressure; MEDG, Mitral end-diastolic gradient; C.I., cardiac index; and PAR, pulmonary arteriolar resistance.
The numbers represent the average values for each group. Normal values for this laboratory are indicated under column headings.
*Numbers in parentheses indicate number of patients who underwent catheterization. "V" waves measured from baseline to peak.
†Indicates difference with significance at $P < 0.05$.

Surgical results and fate of patients

Four patients, 2 each from Groups I and III died without surgery. Thirty-five patients underwent cardiac surgery. A Starr-Edwards prosthesis was employed for all valve replacements.

Seven of 10 patients operated upon in Group I had combined mitral and aortic valve replacements. Three had repair of the mitral regurgitation through a left thoracotomy, one by replacement of the mitral valve, and 2 by attempts to reconstruct the ruptured chordae. All 3 of the latter patients died. In 2 of these cases, the degree of aortic regurgitation was so marked that adequate extracorporeal perfusion could not be maintained and the heart could not be resuscitated at the completion of surgery. The third patient, as well as an additional patient who underwent double valve replacement, died in the immediate postoperative period with a low cardiac output syndrome and respiratory complications. There were 2 late deaths, including one patient who died 2 months postoperatively of an intestinal volvulus and another with a paravalvular aortic leak, hemolytic anemia and an acute abdominal catastrophe of uncertain nature. Four patients are living and well.

Among the 13 Group II patients, 12 had aortic valve replacement and one had repair of a paraprosthetic aortic valvular leak. In all cases, the mitral valve was examined at surgery and judged to be normal so that no mitral repair was performed. Eleven of these individuals survive. One patient died of postoperative pulmonary insufficiency and a second with a myocardial infarction. One of the 11 surviving patients required reoperation for a paravalvular leak. The 11 survivors are doing extremely well with disappearance of the murmur of mitral insufficiency in all.

Of the Group III patients, 10 had double valve replacements and 2 had only a mitral replacement. Three of this group had, in addition, a tricuspid annuloplasty for tricuspid regurgitation. Two patients died postoperatively with a low output syndrome. There were 2 late deaths, one from chronic congestive heart failure 3 months postoperatively and the other from a coronary embolus. The remaining 8 patients are living and doing well.

Thus, of the 35 patients operated upon 23 survived 12 to 60 months postoperatively (average 30 months).

Pathological findings

In Group I, chordae attached to the mitral septal leaflet were ruptured in 9 cases. In one case, the chordae of the mitral mural leaflet were disrupted, and in one case chordae to both leaflets were involved. In one patient, the location of the ruptured chordae is unknown. The leaflets and the remnants of the chordae tendineae were microscopically normal in one case and showed mild fibrosis and thickening in the remainder. The mitral valves in Group III showed chronic rheumatic scarring.

The aortic valve demonstrated deformity and fibrosis consistent with rheumatic disease in 33 of the 35 cases in which it was examined. In one patient with rheumatoid spondylitis and another with lues, the principal changes were those of aortitis. Two patients in Group I and another in Group II had bacterial vegetations on the aortic cusps.

Discussion

Competence of the mitral valve is particularly important in the presence of significant aortic insufficiency. In addition to protecting the pulmonary venous bed from the pressure generated by ventricular contraction, the competent mitral valve also allows maximum left ventricular wall tension to develop.[4] In the presence of very severe aortic regurgitation, left ventricular end-diastolic pressure may actually exceed that of the left atrium, but if the mitral valve is incompetent diastolic mitral regurgitation can occur. Obviously regurgitation through both aortic and mitral valves means considerably more volume work for the heart.

In this series, 3 etiologies for mitral insufficiency complicating aortic regurgitation were delineated as determined by examination of the heart directly at cardiac surgery or autopsy: (1) rupture of the mitral chordae tendineae (Group I); (2) relative mitral insufficiency as a consequence of left ventricular failure (Group

II) and (3) rheumatic mitral insufficiency (Group III) Comparison of the 3 groups reveals a clinical spectrum extending from that of predominant mitral valve disease in Group III to predominant aortic valve disease in Group II Patients with ruptured chordae tendineae occupied a somewhat intermediate position

Groups I and II were characterized by male predominance and relatively short, rapidly progressive histories of congestive failure Sinus rhythm and mild to moderate left atrial enlargement were usually present. Bacterial endocarditis was more frequent in Group I Angina pectoris was more often a troublesome symptom in Group II Physical signs and catheterization evidence of severe aortic regurgitation with left ventricular failure were common in both groups. The patients in Group I manifested particularly rapid clinical deterioration and the tallest "V" waves. However there was considerable overlap in these findings.

Patients with organic mitral insufficiency (Group III) differed from Groups I and II in several respects. Cardiac decompensation was more gradual females predominated and a disproportionately large left atrium with atrial fibrillation was the rule. Clinical and catheterization evidence of aortic insufficiency and left ventricular failure was less striking Mitral valve calcification were frequently observed and angina pectoris and bacterial endocarditis were uncommon.

The close similarities between the first 2 groups, and particularly their rapid deterioration after the onset of symptoms are not surprising In the first group, the abrupt onset of mitral regurgitation from rupture of the chordae tendineae imposed an additional volume load on a heart that was already laboring under the burden of aortic incompetence. In the second group, the appearance of relative mitral insufficiency indicated the presence of severe left ventricular dilatation and failure and also hastened decompensation by superimposing the additional insult of regurgitation through the mitral valve. Thus the appearance of a murmur of mitral regurgitation in a patient with long-standing aortic incompetence is an ominous sign, and ruptured mitral chordae or functional mitral regurgitation should be considered when it arises.

Acute mitral insufficiency seen in Groups I and II was associated with relatively small left atria, preservation of sinus rhythm and the largest 'V' waves in the pulmonary wedge pressure tracings. This was in contrast to chronic mitral insufficiency in Group III who showed generally large left atria, atrial fibrillation, and small 'V' waves. However the height of the 'V' wave, degree of left ventricular failure, and clinical course in Group I did not differ significantly from other patients reported from this hospital with ruptured mitral chordae tendineae without aortic incompetence.[1, 7]

Despite widely incompetent aortic and mitral valves on surgical or postmortem examinations peak systolic aortic gradients and mitral end-diastolic gradients were found not infrequently indicating that some relative obstruction at both sites was present. However mitral gradients were rare in Group II

Reference has been made previously to rupture of the mitral chordae tendineae in association with aortic incompetence, particularly in the presence of bacterial endocarditis.[4] This association was noted in the series of ruptured chordae tendineae previously reported from this hospital We were surprised to find 12 patients with this combination of lesions. The occurrence of bacterial endocarditis in 5 of these individuals makes it likely that infection played a significant role in chordae disruption. However 7 patients showed no evidence of bacterial endocarditis, and rupture of the chordae appeared to have occurred spontaneously The ruptured chordae were predominantly those attached to the septal leaflet of the mitral valve in contrast to the group of ruptured chordae tendineae without aortic insufficiency in whom rupture more often involved the mural leaflet.[7]

The aortic regurgitant jet usually strikes the septal leaflet of the mitral valve. It is possible that continued trauma against the chordae tendineae imposed by this jet as well as rapid recoil of the left ventricle in early diastole as a result of aortic regurgitation may contribute to rupture. Furthermore, as the left ventricle dilates,

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chordae become even further stretched and attenuated. Finally during systole the tension applied by vigorous contraction of the papillary muscles provides additional stress to the chordae. Infection of course renders the chordae even more vulnerable to rupture and trauma to the chordae may predispose to bacterial attack.

Functional mitral insufficiency can be expected to disappear completely after severe aortic incompetence is relieved by valve replacement and the risks and results of surgery are essentially those of solitary aortic valve replacement. In contrast both ruptured chordae tendineae and rheumatic mitral regurgitation will usually necessitate combined aortic and mitral valve replacement with a higher operative risk.

Our surgical approach to patients with combined severe aortic and mitral regurgitation is usually as follows. Before the patient is placed on cardiopulmonary bypass, the presence of associated mitral regurgitation is usually confirmed by palpation of the regurgitant jet against the wall of the left atrium or preferably by direct digital exploration of the mitral valve through the left atrium of the beating heart. The patient is then placed on total cardiopulmonary bypass and the aortic valve replacement is first undertaken. The mitral valve is carefully inspected insofar as possible through the aorta after the aortic valve has been removed. The aortic valve prosthesis is then inserted. If mitral regurgitation seems functional or insignificant after aortic valve replacement the patient is temporarily taken off cardiopulmonary bypass and the left atrium is again explored with the beating heart to assess the severity of the mitral regurgitation. If severe mitral insufficiency persists the mitral valve is exposed and repaired or usually replaced. In our experience, functional mitral insufficiency which may be quite impressive prior to aortic valve replacement, is markedly decreased almost immediately after aortic valve replacement and it has not been necessary to repair the mitral valve in any such case.

Summary

The problem of mitral incompetence complicating aortic regurgitation was analyzed in 39 patients. Three groups were defined according to the etiology of mitral insufficiency. *Group I* (12 patients) rupture of the mitral chordae tendineae. *Group II* (13 patients) mitral insufficiency as a consequence of advanced left ventricular failure and *Group III* (14 patients) organic mitral incompetence. The clinical, hemodynamic and radiographic features of the 3 groups were compared. Groups I and II showed many common features including rapid deterioration after the initial appearance of symptoms. Patients in Group III pursued a more indolent course. Attention is called to the unusual association of aortic insufficiency with ruptured mitral chordae, and factors contributing to chordae disruption are discussed.

Thirty five patients underwent cardiac surgery with 23 long term survivors. Results were best in Group II which behaved surgically much like solitary severe aortic valve disease.

Combined mitral and aortic incompetence imposes a serious hemodynamic burden on the heart. The appearance of mitral insufficiency in patients with aortic insufficiency often necessitates early surgical intervention.

REFERENCES

1. Welch, G. H., J., Braunwald, E., and Sarnoff, S. J.: Hemodynamic effects of quantitatively varied experimental aortic regurgitation, Circulation Res 5:546, 1957.
2. Rees, J. R., Epstein, E. J., Criley, J. M., and Ross, R. S.: Haemodynamic effects of severe aortic regurgitation, Brit. Heart J 26:412, 1964.
3. Wigle, E. D., and LaBrosse, S. J.: Sudden severe aortic insufficiency, Circulation 32:708, 1965.
4. Meadows, W. R., Van Praagh, S., Indreika, M., and Sharp, J. T.: Premature mitral valve closure, Circulation 28:251, 1963.
5. Braunwald, E., and Frahm, C. J.: Studies on Starling's law of the heart. IV. Circulation 24:633, 1961.
6. Sanders, C. A., Scannell, J. G., Harthorne, J. W., and Austen, W. G.: Severe mitral regurgitation secondary to ruptured chordae tendineae, Circulation 31:506, 1965.
7. Sanders, C. A., Austen, W. G., Harthorne, J. W., Dinsmore, R. E., and Scannell, J. G.: Diagnosis and surgical treatment of mitral re-

gurgitation secondary to ruptured chordae tendineae, New England J Med 276:943 1967
8 Edwards, J E., and Burchell, H. B. Pathologic anatomy of mitral insufficiency Proc. Staff Meet. Mayo Clin. 33:497 1958.
9 Edwards, J E., and Burchell, H B. Endocardial and intimal lesions (jet impact) as possible sites of origin of murmurs, Circulation 18:946, 1958.
10. Austen, W G., Kastor J A., and Sanders, C A. Resolution of functional mitral regurgitation following surgical correction of aortic valvular disease, J Thoracic Cardiovas. Surg 53:255, 1967

The effect of the dextro isomer of propranolol on sinus rate and cardiac arrhythmias

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A number of β-adrenergic blocking drugs have been described their potencies differ and some have been shown experimentally to have one or more additional direct actions on the myocardium which are not the result of β blockade These include sympathomimetic and myocardial depressant effects and the abolition of arrhythmias resulting from digitalis intoxication Clearer differentiation between β-blocking and other actions of some of these compounds became possible with the separation of their optical isomers studies of these isomers have shown that the β-blocking action is largely confined to the levo (*l*) isomers, while the myocardial depressant effect is of similar magnitude in both levo and dextro (*d*-) forms.[3-13]

Commercially available propranolol (*dl* propranolol) consists of 50 per cent *d* propranolol and 50 per cent *l*-propranolol *dl* Propranolol is a powerful β-blocking drug[1] it also has depressant effects on heart muscle[1,12,13] and terminates digitalis-induced arrhythmias,[14,16] but has no significant sympathomimetic action.[17] It is widely used clinically in the treatment of cardiac arrhythmias and some of its actions as an antiarrhythmic drug may be due to its direct myocardial effects In this paper we report the effects of *d* propranolol, which has very little β-blocking activity on a group of patients in sinus rhythm or with cardiac arrhythmias, and compare them with the effects of similar doses of *dl* propranolol

The actions of *dl* propranolol on heart rate and arrhythmias[12] can be divided into four main groups, and we have used this classification to present the results with the *d* isomer

Classification

1 Sinus rhythm *dl*-Propranolol reduces the resting rate with a more consistent and pronounced effect on exercise.

2 Atrial fibrillation and flutter *dl* Propranolol reduces the ventricular rate by its action on the atrioventricular node.

3 Ectopic arrhythmias Ectopic arrhythmias other than atrial flutter and fibrillation may be considered together

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(1) Supraventricular (SV) and ventricular ectopic beats, SV tachycardias (i.e. paroxysmal atrial tachycardia or nodal tachycardia) and ventricular tachycardia. *dl*-Propranolol has an inconsistent effect: it may occasionally terminate paroxysmal tachycardias, or reduce or abolish ectopic beats. (2) Ectopic beats induced by exercise or a rebreathing procedure: *dl*-Propranolol usually prevents these ectopic beats.

4 *Digitalis induced arrhythmias*: *dl*-Propranolol reduces or abolishes these arrhythmias.

Material and methods

A total of 84 subjects were studied: 25 who were in sinus rhythm and 59 who had various types of cardiac arrhythmias.

Both *dl*-propranolol and *d*-propranolol were given to most subjects. The drugs were administered intravenously, either given on different days or one given 2 hours or more after the other (the pharmacological half life of *dl*-propranolol is about 40 minutes[7]). Both drugs were usually given at two dose levels and in some subjects more detailed dose-response curves were obtained. An interval of at least 20 minutes elapsed before second or subsequent doses of the same drug were injected. Wherever possible the heart rate and rhythm were recorded every five minutes for at least 30 minutes before any drug was given. After injection the rate and rhythm were recorded for 30 seconds every 5 minutes for at least 20 minutes. All observations on patients with arrhythmias were made from the electrocardiograms. No patient had been given quinidine or any similar antiarrhythmic drug. In the group with atrial fibrillation or flutter all except 3 patients were receiving maintenance digitalis therapy.

1 *Sinus rhythm (25 subjects)*

(A) 6 NORMAL SUBJECTS The heart rate was counted at rest and for 15 seconds beginning 10 seconds after cessation of a fixed period of standard exercise. After 3 control periods of exercise, 0.25, 1.0 and 4.0 mg of *dl*-propranolol were injected and exercise was performed after each dose. The resting heart rate was counted immediately before and 10 minutes after each injection. The subjects rested for 30 minutes after exercise, the drug was injected and they exercised again 10 minutes later. The following week the whole procedure was repeated with 1, 4 and 16 mg of *d*-propranolol.

(B) 19 PATIENTS In this group were: normal heart 6, rheumatic heart disease (H.D.) 4, hyperthyroidism 4, hypothyroidism 1, ischemic H.D. 2, sinus tachycardia of unknown cause 2. When the effect of either drug was assessed the lowest rate recorded in the control period was compared with the lowest rate attained in the 20 minutes following injection.

2 *Atrial fibrillation (14 patients) and atrial flutter (6 patients)* In this group were: rheumatic H.D. 9, ischemic H.D. 8, lone atrial fibrillation 2, congenital H.D. 1. The ventricular rate was recorded on the electrocardiograph in all cases. The lowest ventricular rate recorded in the control period was compared with the lowest rate attained in the 20 minutes following injection.

3 *Ectopic arrhythmias (33 patients)* In this group were: rheumatic H.D. 9, ischemic H.D. 12, no underlying H.D. 9, renal failure 2, congenital H.D. 1. Digitalis was not considered to be a contributing factor in any of these arrhythmias.

(A) SUPRAVENTRICULAR (SV) (14 PATIENTS)

(1) Ectopic beats (6 patients) The frequency of ectopic beats was expressed as a percentage of the total number of ventricular beats over a 30 second period. The lowest percentages before and after the drug were compared.

(2) Tachycardias (8 patients) In this group were: nodal tachycardia, 2; SV tachycardia, 2:1 AV block, and right bundle branch block, 1; SV tachycardia, 2:1 AV block, 3; repetitive SV tachycardia, 1; repetitive SV tachycardia with intraventricular conduction defect, 1.

(B) VENTRICULAR (15 PATIENTS)

(1) Ectopic beats (13 patients) The effects of the drugs were evaluated as for SV ectopic beats.

(2) Tachycardia (2 patients)

(C) ECTOPIC ARRHYTHMIAS ACCENTUATED BY (1) A REBREATHING PROCEDURE, DESCRIBED IN DETAIL ELSEWHERE (PATIENTS) OR (2) EXERCISE (2 PATIENTS)

(1) In a small proportion of patients who

experience ventricular ectopic beats spontaneously rebreathing into a bag containing 2 L. of oxygen up to the limit of tolerance leads to an appreciable increase in the percentage of ventricular ectopic beats immediately after disconnecting the bag. This increase can be abolished by a previous injection of *dl*-propranolol. Two patients with ventricular ectopic beats were studied. Neither patient had any disease involving the lungs. The rebreathing procedures were carried out before and after the administration of *d* propranolol.

(2) *d* Propranolol and *dl* propranolol were given 10 minutes before exercise in 2 patients. One was in sinus rhythm at rest; there were very frequent SV ectopic beats during exercise. The other patient had SV tachycardia with 2:1 AV block at rest and 1:1 ventricular responses with intraventricular conduction defect on exercise.

Results

1 Sinus rhythm

(A) EXERCISE STUDIES. The results are shown in Table I. There was a significant fall in exercise heart rate with 1 and 4 mg. of *dl*-propranolol ($p < 0.01$). Doses of up to 16 mg. of *d*-propranolol produced no significant reduction in exercise heart rate.

*Table I. Effect of dl- and d-propranolol on exercise heart rate in 6 normal subjects**

	Dose (mg.)	Exercise heart rate (per cent of control)	S.D.	S.E.	t
dl-Propranolol	0.25	100.5†	5.3	2.2	−0.2
	1.0	92.2†	5.7	2.3	3.3
	4.0	88.2†	6.8	2.8	4.2
d Propranolol	1.0	100.9‡	3.8	1.6	−0.6
	4.0	99.6‡	6.5	2.7	0.2
	16.0	97.4‡	7.8	3.2	0.8

*Experiment with *d*-propranolol performed one week after the with *dl*-propranolol. On each occasion the mean heart rate after 3 control periods of exercise in 6 subjects is taken as 100 per cent. The mean heart rate after exercise for the 6 subjects following each injection of the drug is compared with this control value.
†100 per cent = 147.8 per minute.
‡100 per cent = 140.5 per minute.

(B) EFFECT ON RESTING SINUS RATE. A fall of 5 per cent or less in the resting level was arbitrarily considered a nil response, 5 to 10 per cent an equivocal response, and a fall of over 10 per cent a definite response.

The results in these 19 patients are summarized in Fig. 1. There was a definite slowing in 15 patients with doses of up to 10 mg. of *dl* propranolol but in only 2 with comparable doses of *d*-propranolol.

Detailed comparisons of the effects of the two drugs in 2 patients are shown in Figs. 2 and 3 and illustrate the greater potency of *dl* propranolol in slowing sinus rate.

2 Atrial fibrillation and flutter. The ventricular rate was counted before and after each dose. The responses were graded as for sinus rhythm. The results in 20 patients are summarized in Fig. 4. There was a definite reduction in ventricular rate in all cases after 10 mg. or less of *dl* propranolol but in only 5 cases when *d* propranolol was given in approximately the same dose range. There was a definite response in a

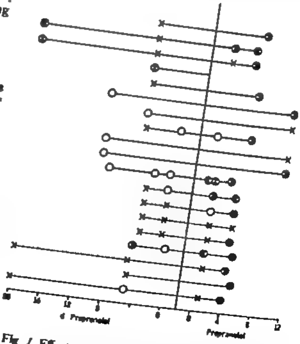

Fig. 1. Effect of *dl*- and *d*-propranolol on patients in sinus rhythm at rest. Each horizontal line represents a patient; the doses of each drug are shown on the scale at the base. Clear circle, heart rate not reduced or reduced by less than 5 per cent; X, heart rate reduced by 5 to 10 per cent; circled X, heart rate reduced by more than 10 per cent.

further 2 patients when given 20 mg of *d* propranolol. More detailed comparisons of the effects of the two drugs are shown in Figs. 5 and 6 and indicate the more potent effect of *dl* propranolol in slowing ventricular rate. No difference in the response was observed between atrial flutter and atrial fibrillation.

3 *Ectopic arrhythmias*

(A) SUPRAVENTRICULAR. The results are shown in Fig. 7

(1) Ectopic beats. If the frequency of

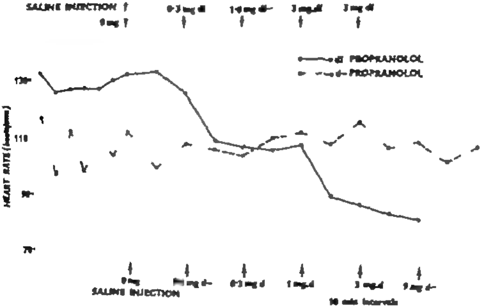

Fig. 2 The effect of *d*- and *dl*-propranolol on sinus rate in a patient with sinus tachycardia of unknown cause. Drugs given on different days.

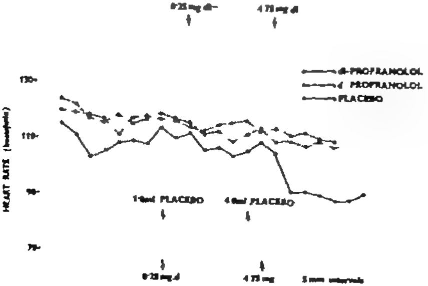

Fig. 3 The effect of *d*- and *dl*-propranolol and placebo on the sinus rate of a patient with hyperthyroidism. Drugs and placebo given on different days.

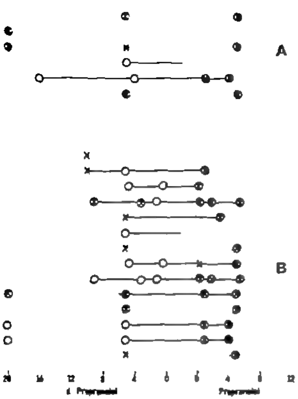

Fig 4 Effect of *dl*- and *d*-propranolol on patients with trial flutter (*A*) and trial fibrillation (*B*) Clear circle, ventricular rate not reduced or reduced by less than 5 per cent X, ventricular rate reduced by 5 to 10 per cent circled X, ventricular rate reduced by more than 10 per cent.

ectopic beats was unaffected or reduced by less than 25 per cent this was considered a nil response If it was reduced by 25 to 50 per cent this was an equivocal response if it was reduced by more than 50 per cent or the ectopic beats were abolished completely this was regarded as a definite *response*.

Four patients were given both *dl* propranolol and *d* propranolol There was a definite response in 2 to similar doses of each drug there was a definite response in 2 to *dl* propranolol but an equivocal response to the same dose of *d* propranolol

In the 2 patients who were given only *d* propranolol there was a definite response to 5 mg in both cases.

(2) Tachycardias. Neither drug had any effect in 6 of 8 patients. In the remaining 2 the arrhythmias were modified but not abolished One patient initially had nodal tachycardia and this was changed to slow nodal rhythm In the other patient, each sinus beat was followed by multiple irregular atrial ectopic beats after 20 mg of *d* propranolol each sinus beat was followed by two SV ectopic beats with aberration and then a short run of regular SV tachycardia.

(B) VENTRICULAR. The results are summarized in Fig 8

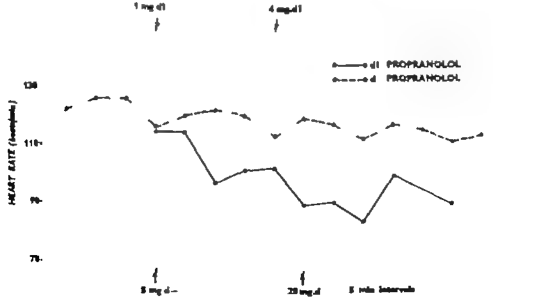

Fig 5 The effect of *d* and *dl*-propranolol on the ventricular rate of patient with idiopathic trial fibrillation. Drugs given on different days.

(1) Ectopic beats. In 4 patients, neither *dl*-propranolol nor *d*-propranolol had an effect in a dose of 5 mg or less, but in one patient 20 mg of *d* propranolol had a definite effect. Another 5 patients were given only *d*-propranolol and the drug was ineffective in all 5 Three patients had definite responses to the same doses of *dl* and *d* propranolol and a fourth showed an equivocal response to *d* propranolol and no response to *dl*-propranolol.

(2) Tachycardias. There were 7 patients in this group One did not respond to either drug the other was given only *d*-propranolol and did not respond

(C) ECTOPIC ARRHYTHMIAS ASSOCIATED WITH REBREATHING OR EXERCISE

(1) Rebreathing The results are shown in Table II A dose of 5 mg of *d*-propranolol partially suppressed the increase in ectopic beats in one patient and then 20 mg of *d* propranolol completely suppressed them. In the other patient, 10 mg of *d*-propranolol completely suppressed the increase in ectopic beats.

(2) Exercise. In the patient who developed very frequent SV ectopic beats on exercise, neither *dl* propranolol nor *d* propranolol had any effect. In the other patient with 1 1 atrial tachycardia and frequent aberration on exercise 5 mg of *d*-propranolol was given after the drug the rhythm during exercise was 2 1 atrial tachycardia with no aberration.

In summary in the ectopic arrhythmias *dl* and *d*-propranolol either had no effect or had approximately equivalent effects.

4 *Digitalis arrhythmias* Only *d*-propranolol was given to the 6 patients studied In the 3 patients with bigeminy a dose of 5 mg abolished the arrhythmia. The effect was temporary in 2 patients it lasted for 30 seconds after 5 mg and for 5 minutes after 20 mg in one patient and for 20 minutes after 5 mg in the other

The patient with 2 1 atrial flutter and frequent ventricular ectopic beats was given 5 mg the ventricular rate was slowed and the ectopic beats became less frequent.

The atrial tachycardias were abolished in both patients, in one with 5 mg and in the other with 20 mg of *d* propranolol

Side effects

There were no side effects in any instance after the administration of *d*-propranolol doses of up to 20 mg were given. Three patients however had adverse reactions when *dl*-propranolol was given after *d*-propranolol. These incidents are described briefly below the second and third patients are not included in the present series be

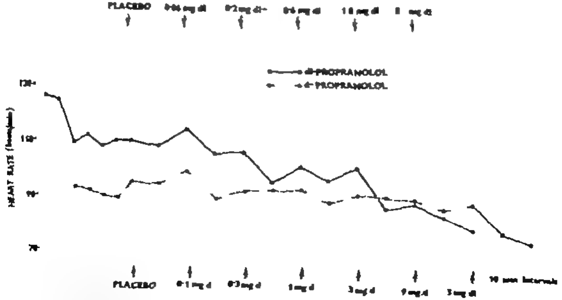

Fig. 4 The effect of *d* and *dl*-propranolol on the ventricular rate of patient with mitral stenosis and trial fibrillation. Drugs given on different days.

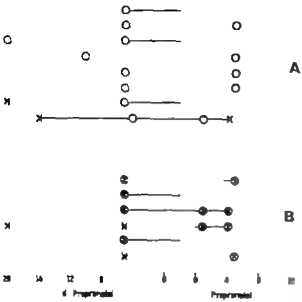

Fig 7 Effect of dl and d-propranolol on patients with supraventricular tachycardias (A) and supraventricular ectopic beats (B). A clear circle, not affected X, modified but not abolished. B clear circle, ectopics not affected or reduced by less than 25 per cent X, ectopics reduced by 25 to 50 per cent circled X, ectopics reduced by more than 50 per cent or abolished completely

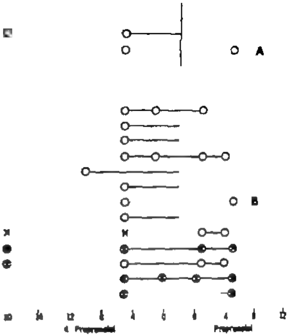

Fig 8 Effect of dl- and d-propranolol on patients with ventricular tachycardias (A) and ventricular ectopic beats (B). A clear circle, no effect. B clear circle ectopics not affected or reduced by less than 25 per cent X, ectopics reduced by 25 to 50 per cent circled X, ectopics reduced by more than 50 per cent or abolished completely

cause dl propranolol was given at such a short interval after d-propranolol.

Case 1 M C., 38-year-old woman had hypertensive and ischemic heart disease. She was admitted with ventricular tachycardia of 3 days duration. A 5 mg dose of d-propranolol was given It had no effect on the arrhythmia and no side effects. An hour later 5 mg. of dl-propranolol was given t had no effect on arrhythmia but 5 minutes later th patient became pale, sweaty and hypotensive. She recovered after 15 minutes and subsequently was successfully treated with D C. countershock.

Case 2 W R., 41 year-old woman had infundibular hypertrophic subaortic stenosis (IHSS). She was seen one hour after the onset of rapid trial fibrillation. A 5 mg dose of d-propranolol was given, and 20 minutes later further dose of 20 mg There was slowing of the ventricular rate from 190 to 160 per minute, and no side effect. Half n hour later 1 mg of dl-propranolol was given the ventricular rate was reduced to 140 per minute and the patient remained well. Twenty min tes later she was given 4 mg of dl-propranolol 20 minutes after this dose, there was an brupt return to sinus rhythm the patient lost consciousness transiently became pale, and sweated. She recovered over 15 minutes.

Case 3 F S., a 32-year-old man, had mitral stenosis, severe pulmonary hypertension and sinus tachycardia (125 per minute) He was given d and dl-propranolol during investigation of the left side of the heart. A 10 mg dose of d-propranolol was given, nd had no hemodynamic effect. Twenty minutes later a 10 mg dose of dl-propranolol was given 7 minutes fterwards the patient lost consciousness, with a profound fall in LV pressure, dp/dt, nd cardia output. The heart rate was 75 per minute. H recovered over the following 30 minutes.

Comment The adverse reactions in these 3 patients may have been due to the cumulative myocardial depressant effect of d and dl propranolol. It seems more likely however that d propranolol was innocuous and the adverse effects were the result of β blockade. Both factors may have played a part. A further factor in the patient with IHSS may have been an increase in the outflow tract obstruction from the sudden resumption of slow sinus rhythm

The 8 patients with digitalis intoxication were given only d propranolol Five were in congestive heart failure and there was no deterioration after d-propranolol in any instance.

*Table II. Effect of d propranolol on the increase in ventricular ectopic beats resulting from a rebreathing procedure (see text)**

Patient	Ectopics (per cent)	Pressure of CO_2 in bag (mm. Hg)
A		
Basal	0	
First rebreathe (control)	40	56
Basal	0	
Second rebreathe (after 5 mg. of *d*-propranolol)	8	60
Basal	0	
Third rebreathe (after 20 mg. of *d*-propranolol)	[illegible]	68
B		
Basal	19	
First rebreathe (control)	30	[illegible]
Basal	23	
Second rebreathe (after 10 mg. of *d*-propranolol)	7	58

*The incidence of ectopic beats is stated as a percentage of the total number of ventricular beats over the 30 second period following disconnecting the bag.

Two patients with severe obstructive disease of the airways were given only *d*-propranolol. There was no clinical deterioration. Forced expiratory volume in 1 second (FEV) and forced vital capacity (FVC) were measured before and at frequent intervals after the drug and showed no change.

Discussion

Sinus rhythm, atrial fibrillation and flutter. A number of workers[4,19,23] have shown that *d*-propranolol has very little β-blocking activity compared with the racemate. Howe and Shanks[19] reported that *dl*-propranolol was 60 to 100 times more potent than its dextro isomer in blocking the inotropic and chronotropic effects of isoprenaline. In our study, *d* propranolol was clearly less effective than *dl*-propranolol in slowing the sinus rate and reducing the ventricular rate in patients with atrial fibrillation and flutter. Thus it seems likely that these actions of *dl* propranolol on the sinus and AV nodes are predominantly or entirely through β blockade.

Ectopic arrhythmias spontaneous or induced by rebreathing or exercise. In patients with spontaneous SV and ventricular ectopic beats and tachycardias, either *dl* and *d*-propranolol were both ineffective or they had approximately equivalent effects. It is therefore unlikely that the action of *dl* propranolol in these ectopic arrhythmias is predominantly through β blockade. It must be by some action other than β blockade which is present in the dextro isomer.

dl Propranolol reduces the height and rate of rise of the action potential, prolongs the effective refractory period, and has an antifibrillatory effect on atrial muscle.[8-20] Vaughan Williams[21] regarded these actions as distinct from β blockade and similar to those possessed by local anesthetic drugs including procaine amide and quinidine although there are differences in potency between local anesthetic action, antifibrillatory effect, and modification of intracellular potentials. Other workers[4,22,24] have shown that *dl* propranolol has both negative inotropic and chronotropic effects on the myocardium which are not the result of β blockade.

Although *d* propranolol is far less potent than *dl* propranolol as a β-blocking drug, studies to date indicate that the two compounds are equipotent in their other actions on cardiac muscle. They are equally effective in prolonging the refractory period of electrically driven left atria, and have equivalent direct negative inotropic and chronotropic effects on cat papillary muscle and right atrial preparations.[22] *d* Propranolol has a local anesthetic action.[22] There results indicate the kind of ways, distinct from β blockade, in which propranolol acts in ectopic arrhythmias.

It seemed reasonable to postulate[24] that the arrhythmias provoked by exercise, a rebreathing procedure, and anesthesia were mediated through sympathetic stimulation and that they were abolished by the β-blocking action of *dl* propranolol. It was surprising to find, therefore, that the dextro isomer was effective in preventing arrhythmias due to rebreathing and exercise. The number of cases studied was too small to be significant but the results do suggest that

dl propranolol is not acting solely as a β blocker in these cases. It is of interest in this respect that Howe and Shanks[19] found that *dl*-propranolol was only ten times more potent than the dextro isomer in abolishing halogen-epinephrine arrhythmias, and Lucchesi[23] reported that *dl*-pronethalol and its dextro isomer were equally effective against anesthetic-epinephrine arrhythmias. More recently however he found *d* propranolol (5.0 mg per kilogram) failed to prevent epinephrine induced arrhythmia in dogs.[24]

Digitalis-induced arrhythmias The effectiveness of small doses of *d* propranolol against arrhythmias due to digitalis intoxication suggests that this action of *dl*-propranolol also is not through β blockade Howe and Shanks[1] showed that the levo isomer had very little effect on experimentally produced digitalis arrhythmias in animals whereas the dextro and racemic forms were equally potent, although the doses necessary were relatively far greater than those used clinically More recently Barrett and Cullum[27] have shown that the *levo isomer does have antidigitalis properties.*

Therapeutic implications When *dl* propranolol is used to reduce the sinus rate or the ventricular rate in patients with atrial fibrillation or flutter its action is dependent on the β-blocking properties of the drug When it is used to suppress or abolish ectopic beats tachycardias or digitalis arrhythmias, however the β-blocking action appears to play little or no part. Indeed β blockade may have deleterious effects in reducing sympathetic drive to the heart. The dextro isomer is therefore a potentially useful drug in the management of these arrhythmias and warrants further study In our limited experience, existing heart failure or obstructive disease of the airways were not aggravated by the drug Pharmacologically *d* propranolol has similar actions to quinidine procaine amide and lidocaine but recent work with animals[22] suggests that it may have some therapeutic advantages over quinidine.

Summary

Previous workers have shown experimentally that *dl* propranolol in addition to its β-blocking action has a direct depressant effect on cardiac muscle and terminates arrhythmias due to digitalis overdosage. The dextro isomer of propranolol has very little β blocking activity compared with *dl* propranolol but has an equivalent direct myocardial action In this investigation *d*-propranolol and in most cases *dl*-propranolol also was given to 25 patients in sinus rhythm and 59 with cardiac arrhythmias. *d* Propranolol had much less effect than *dl* propranolol on sinus rate and on ventricular rate in atrial flutter and fibrillation. In supraventricular and ventricular ectopic beats and tachycardias however either both drugs were ineffective or they had approximately equivalent effects. *d* Propranolol terminated digitalis arrhythmias. It is suggested from these observations that the actions of *dl* propranolol on the sinus node and on the atrioventricular node in atrial flutter and fibrillation are through β blockade. In other ectopic arrhythmias and in digitalis intoxication its action is by a mechanism or mechanisms other than β blockade

D J Rowland and M Hussain were in receipt of grants from the Research Grants Committee, United Manchester Hospitals We are indebted to I C.I Pharmaceuticals for generous supplies of *d*-propranolol.

REFERENCES

1 Powell C E. and Slater I H Blocking of inhibitory adrenergic receptors by dichloro analog of isoproterenol, J Pharmacol & Exper Therap. 122:480 1958.
2. Black, J W and Stephenson J S. Pharmacology of a new adrenergic beta-receptor blocking compound (Nethalide), Lancet 2:311, 1962.
3. Black, J W Crowther A. F Shanks, R. G., Smith, L. H. and Dornhorst, A. C. A new adrenergic beta-receptor antagonist, Lancet 1 1080, 1964
4 Lish, P M Weikel, J H and Dungan K. W: Pharmacological and toxicological properties of two new β-adrenergic receptor antagonists, J Pharmacol. & Exper Therap. 149 161 1965.
5 Pharmacological studies on H 56/28—a new β-adrenergic receptor antagonist, Acta pharmacol (Kbh.) 25 (suppl. 2): 1967
6. Barrett A. M Crowther A. F Dunlop, D Smith, L. H and Shanks, R. G. Cardio-selective beta blockade. Naunyn-Schmiedeberg Arch. exper Path. & Pharmakol. In press
7 Grandjean, T and Rivier J L. Effets hémodynamiques des inhibiteurs des récepteurs adrénergiques-bêta pendant le cathétérisme cardiaque comparaison entre le propranolol ("Inderal") et la substance CIBA 39089 BA Cardiologia (Basel) 49 139 1966.

8. Levy, J. V., and Richards, V.: Inotropic and chronotropic effects of a series of β-adrenergic blocking drugs: some structure-activity relationships, Proc. Soc. Exper. Biol. (N. Y.) 122:373, 1966.
9. Howe, R.: Structure activity relationships of some β-adrenergic blocking agents, Biochem. & Pharmacol. 12:85, 1963.
10. Howe, R., and Shanks, R. G.: Optical isomers of propranolol, Nature (Lond.) 210:1336, 1966.
11. Levy, J. V.: Relation between β-adrenergic blocking potency and cardiotoxicity in a series of β-adrenergic receptor blocking drugs, Am. J. Cardiol. 19:139, 1967.
12. Whitsitt, L. S., and Lucchesi, B. R.: The cardiac beta-adrenergic receptor blocking actions of propranolol and its stereoisomers, Life Sci. 6:939, 1967.
13. Levy, J. V., and Richards, V.: Inotropic and metabolic effects of three beta-adrenergic receptor blocking drugs on isolated rabbit left atria, J. Pharmacol. & Exper. Therap. 150:361, 1965.
14. McInerny, T. K., Gilmour, D. P., and Blinks, J. R.: Comparison of effects of propranolol and other cardiac adrenergic blocking agents on inotropic and chronotropic actions of catecholamines, Fed. Proc. 24(2)Pt. 1:712, 1965.
15. Turner, J. R. B.: Propranolol in the treatment of digitalis-induced and digitalis-resistant tachycardias, Am. J. Cardiol. 18:450, 1966.
16. Wolfson, S., Robbins, S. L., and Krasnow, N.: Treatment of cardiac arrhythmias with beta-adrenergic blocking agents. Clinical and experimental studies, Am. Heart J. 72:177, 1966.
17. Black, J. W., Duncan, W. A. M., and Shanks, R. G.: Comparison of some properties of pronethalol and propranolol, Brit. J. Pharmacol. 25:577, 1965.
18. Rowlands, D. J., Howitt, G., and Markman, P.: Propranolol (Inderal) in disturbances of cardiac rhythm, Brit. M. J. 1:891, 1965.
19. Morales-Aguilerá, A., and Vaughan Williams, E. M.: The effects on cardiac muscle of beta-receptor antagonists in relation to their activity as local anesthetics, Brit. J. Pharmacol. 24:332, 1965.
20. Benfey, B. G., and Varma, D. R.: Anti-sympathomimetic and antifibrillatory effects of pronethalol and propranolol, Brit. J. Pharmacol. 26:3, 1966.
21. Vaughan Williams, E. M.: Mode of action of beta receptor antagonists on cardiac muscle, Am. J. Cardiol. 18:399, 1966.
22. Parmley, W. W., and Braunwald, E.: Comparative myocardial depressant and anti-arrhythmic properties of d-propranolol, dl-propranolol and quinidine, J. Pharmacol. & Exper. Therap. 158:11, 1967.
23. Shanks, R. G.: Unpublished observation, 1967.
24. Howitt, G.: The role of beta-adrenergic blocking agents in cardiac therapy, in Symposium of disorders of the heart and circulation, Edinburgh, 1966, Royal College of Physicians, p. 136.
25. Lucchesi, B. R.: The effects of pronethalol and its dextro-isomer upon experimental cardiac arrhythmias, J. Pharmacol. & Exper. Therap. 148:94, 1965.
26. Lucchesi, B. R., Whitsitt, L. S., and Stickney, J. L.: Anti-arrhythmic effects of beta adrenergic blocking agents, Ann. New York Acad. Sc. 139:940, 1967.
27. Barrett, A. M., and Cullum, V. A.: In preparation.

The clinical usefulness of the amyl nitrite inhalation test in the assessment of the third and atrial heart sounds in ischemic heart disease

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Currently there is much interest in establishing methods for the evaluation of myocardial reserve function in patients with ischemic heart disease through exercise tests or use of various pharmacological agents. We have a particular interest in the third and atrial sounds and have recently demonstrated their diagnostic usefulness in ischemic heart disease through exercise phonocardiograms. As a further evaluation of the relationship between diastolic heart sounds and hemodynamic events in this disease, we have observed the effect of amyl nitrite on the third and atrial sounds in normal subjects and those with ischemic heart disease.

Although amyl nitrite is widely applied in the assessment of cardiac murmurs, the effect of this drug on the diastolic heart sounds has not been systematically evaluated.

It is the purpose of this report, therefore, to discuss the clinical applicability of the amyl nitrite inhalation test with special reference to the third and atrial sounds in patients with ischemic heart disease.

Subjects

A total of 106 male subjects over 40 years of age were selected and divided into 3 groups.

Group A included 20 patients with previously documented myocardial infarction or angina pectoris but without obvious evidence of congestive heart failure. All patients had definite evidence of left ventricular ischemia on electrocardiogram (ECG).

Group B consisted of 32 hypertensive patients with diastolic blood pressure over 95 mm Hg but without any electrocardiographic signs of left ventricular ischemia.

Group C included 54 normal, healthy individuals without clinical manifestations of cardiovascular disease.

Patients with any type of arrhythmias or a significant heart murmur suggesting the presence of valvular heart disease or congenital cardiac malformation were excluded from this study.

Methods

All subjects were studied following a 30-minute period of bed rest. A low-fre-

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quency (30 to 120 cycles per second) phonocardiogram was recorded at the apical area. Recordings were made simultaneously with Lead V_1 ECG at a paper speed of 50 mm. per second through a direct writing 2-channel oscillograph with the subjects in the supine position during mid-expiratory apnea. The gain setting of the phonocardiograph was the same for each subject all through the test. After the control tracing consecutive recordings were obtained at 15-second intervals for 2 minutes after completion of amyl nitrite inhalation. Each subject was encouraged to take deep inhalation of the amyl nitrite vapor 5 times from a broken ampule. Blood pressure was measured in the left upper extremity at the same time intervals.

Five patients in Group II had a right heart catheterization done with the amyl nitrite inhalation test so that the changes in the diastolic sounds might be correlated with left atrial pressure as reflected in pulmonary capillary wedge (PCW) pressure.[3]

The following measurements were made in each part of each tracing amplitude of the first second third and atrial sounds on the phonocardiogram R R interval S-T segment and T wave changes on the ECG In those patients in which PCW pressure was available, the amplitude of the pressure waves (c, v and a) was also measured

The amplitudes and intervals were expressed in millimeters based on the average of 5 consecutive cardiac cycles.

Results

Fig 1 shows the amplitude changes of the third and atrial sounds before and after amyl nitrite inhalation in the 3 groups. Each line represents the average value of both sounds in each group. In the heart disease group, a remarkable augmentation of both diastolic sounds started at approximately 15 seconds and had its peak at 45 seconds after completion of inhalation. Then, the amplitude progressively decreased, approaching control levels at 120 seconds. In the other 2 groups (normal and hypertensive subjects) no definite postinhalation changes were found except for a minimal variation in amplitude. There was

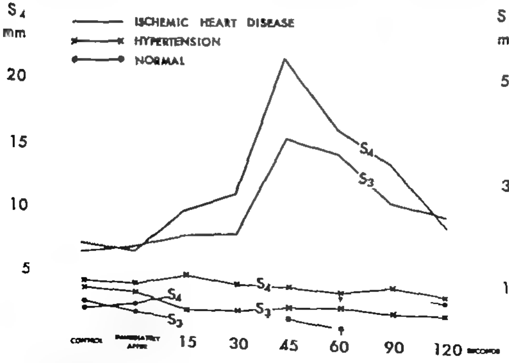

Fig 1 The amplitude changes of the third and atrial heart sounds in the average value of the 3 groups before and after amyl nitrite inhalation test. S_3, Third heart sound. S Atrial heart sound.

Table I. The behavior of the third and atrial sounds after amyl nitrite inhalation test in the 3 groups

Groups	Cases studied	No. of cases with definite increase in amplitude after the test		
		Either or both diastolic sound	Third sound only	Atrial sound only
Ischemic heart disease	20	11 (55%)	3	11
Hypertension	32	3 (9%)	1	3
Normal healthy	54	2 (4%)	0	2

At least a threefold increase in amplitude over control tracings.
Some cases showed an increase in both third and atrial sounds. Each of these was counted as one case.

no significant difference in the behavior of the diastolic sounds between these 2 groups throughout the test.

Table I summarizes the changes in the third and atrial sounds in the 3 groups after inhalation. Of the 20 patients with ischemic heart disease, 11 (55 per cent) had a significant postinhalation increase in either or both diastolic sounds showing at least a threefold increase in intensity over the control tracing. In the hypertensive group only 3 (9 per cent) had a definite amplitude increase after the test. Of the 54 subjects in the normal group, a postinhalation increase in the diastolic sounds was found in 2 cases (4 per cent).

The amplitude changes of the first and second heart sounds and the R-R interval changes are shown in Fig. 2. Immediately following the start of inhalation, the first heart sound increased proportionately in all three groups. The second heart sound, on the other hand, had a definite decrease in its intensity after the test, but there were again no significant differences between the 3 groups. A sharp decrease in the R-R interval was observed at 15 and 30 seconds in all groups. The maximal deviation of this interval, however, occurred 15 to 30 seconds earlier than the maximal amplitudes of the diastolic sounds seen in the heart disease group.

Fig. 3 represents the average blood pressure in each group. No differences were noted in the effect of amyl nitrite among the studied groups. The maximal drop in blood pressure occurred immediately after completion of inhalation, earlier than the period of the maximal deviation of the diastolic sounds in the heart disease group. A recovery in blood pressure level with some rebound hypertension was observed in the heart disease subjects at 45 seconds, coincident with the peak of postinhalation amplitude of the diastolic sounds.

One of the typical amyl nitrite phonocardiograms is shown in Fig. 4. The top tracing was obtained from a patient with an old myocardial infarction and shows a marked increase in both third and atrial sounds at 45 seconds. The bottom tracing was taken from a normal individual and demonstrates no appreciable change in the diastolic components through the test. In addition to the phonocardiographic findings, the ECG of the patient revealed a T wave inversion in the control tracing becoming flat following amyl nitrite inhalation. In the normal subject, inversely, the T wave which was upright before the test became lower after the test.

Definite postinhalation changes were found in the ECG's of all 3 groups. The directions of T wave deviation following amyl nitrite administration, however, were variable among the 3 groups. Some subjects showed a decrease in amplitude, flattening or inversion, while others showed an increase in amplitude of the T wave. Although there were some S-T segment changes, no particular pattern was evident in any one group.

The change of the PCW pressure level following amyl nitrite inhalation is shown in the average values of 5 hypertensive patients (Fig. 5). The PCW pressure decreased during the test, as shown by a fall in these values. There was no postinhalation augmentation of the diastolic heart sounds in any one of these patients.

Comments

A striking increase in the amplitude of the diastolic heart sounds was found in the patients with ischemic heart disease after

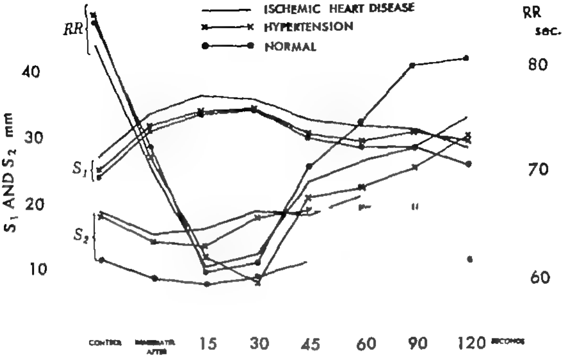

Fig 2 The amplitude changes of the first and second heart sounds and the R-R interval change in the average value of the 3 groups before and after amyl nitrite inhalation test S_1 First heart sound S_2 Second heart sound.

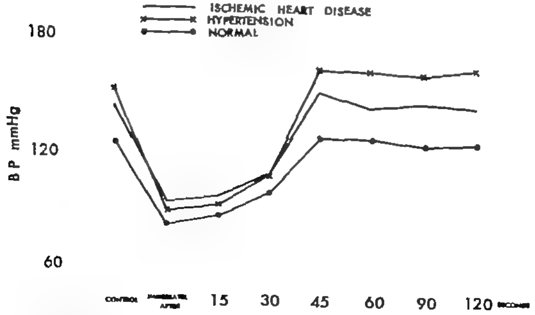

Fig 3. The change of the blood pressure level in the average value of the 3 groups before and after amyl nitrit inhalation test. B.P Blood pressure.

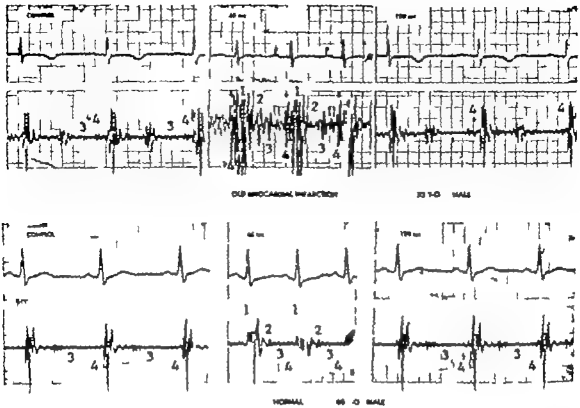

Fig. 4 The phonocardiographic changes before and after amyl nitrite inhalation test. The top tracing 52 year-old man with an old myocardial infarction showing a remarkable increase in both third and atrial sounds after the test. The bottom tracing, a 60-year-old healthy man without significant change in the diastolic components through the test. *1* First heart sound. *2* Second heart sound. *3* Third heart sound. *4* Atrial heart sound.

the amyl nitrite inhalation test. Moreover there was a significant difference in the type of response to this drug in the heart disease patients and in the subjects of the other 2 groups.

The mechanism responsible for these changes is not definitely clear. However it is known that amyl nitrite increases cardiac output as a result of reflex tachycardia and subsequently augments venous return but also produces a sharp drop in systemic blood pressure due to arteriolar dilatation.[9]

In our study a constant increase in the amplitude of the diastolic sounds was observed up to 45 seconds following completion of amyl nitrite inhalation. This corresponds to the period of increasing cardiac output and venous return to the heart.[9] This pattern was also found to be similar both in contour and timing to that described by Mason and Braunwald[14] who showed an elevation of mean forearm blood flow in normal subjects during this same period following the inhalation of amyl nitrite. Accordingly it is possible that the increase in cardiac output and venous return following amyl nitrite administration may exaggerate the diastolic heart sounds because of a volume load to the impaired myocardium in patients with ischemic heart disease. It has been reported by others that a temporary increase in the atrial sounds occurs in some patients with hypertensive heart disease following intravenous aminophylline. This was explained as the result of increased cardiac output.[1] A sudden increase in venous return induced by intravenous saline infusion causes an intensification of the atrial sounds in heart failure subjects.[22]

In our study we observed that coincident with the time of the maximal intens

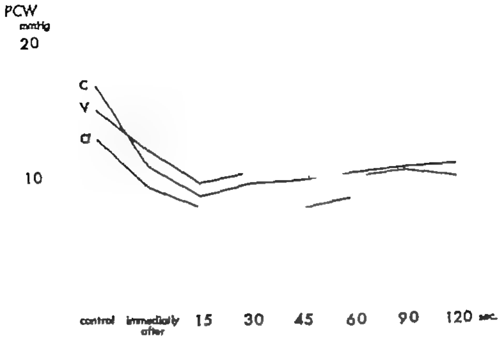

Fig. 5. The change of the pulmonary capillary wedge pressure in the average value of 5 hypertensive patients before and after amyl nitrite inhalation test. *PCW* Pulmonary capillary wedge pressure.

ties in the diastolic sounds, the blood pressure returned to its control levels with occasionally demonstrated rebound hypertension. This rapid hemodynamic load might also be an additional factor causing augmentation of the diastolic sounds in patients with ischemic heart disease. It has been postulated that a rapid rise of arterial blood pressure following a cold pressor test augments the atrial sounds in hypertensive heart disease patients.[22]

Another mechanism which may play a role is the production of coronary insufficiency following amyl nitrite inhalation. An initial striking drop in blood pressure and a concomitant rise in heart rate may reduce coronary blood flow and induce myocardial ischemia in patients with coronary artery disease and may thus intensify the diastolic heart sounds. Contro and associates[16] observed that 45 per cent of patients with coronary artery disease developed an ischemic electrocardiographic change after amyl nitrite inhalation. Additionally, in most patients subjected to both the Master's exercise test and amyl nitrite inhalation the ischemic ST-T changes were similar. In our previous study we reported that the Master's two-step test significantly increased the amplitude of the diastolic heart sounds in patients with ischemic heart disease. However, the present study failed to reveal a good correlation between ischemic electrocardiographic changes and augmentation of the diastolic heart sounds.

Although amyl nitrite is well known for its use in evaluation of heart murmurs in patients with valvular heart disease and congenital cardiac malformations, little information is available concerning the effect on the heart sounds and other hemodynamic events in ischemic heart disease. Kincaid-Smith and Barlow[4] have studied the response to amyl nitrite of the atrial sound in various cardiac conditions. They found that amyl nitrite definitely diminished the atrial sound in hypertensive patients but did not diminish this sound in ischemic heart patients, and that although this drug usually relieves ischemic pain it did not alter the character of the atrial sound in patients with ischemic heart disease who often develop an atrial sound during an attack of anginal pain. In our study we also found a significant differ-

ence in the behavior of the diastolic sounds during the amyl nitrite test between the ischemic heart disease patients and the hypertensive patients. Amyl nitrite definitely increased the diastolic sounds in the former group but did not change them in the latter or in the normal group. No single case in the hypertensive patients selected for this study showed electrocardiographic evidence of myocardial ischemia. Thus, the difference found here and also by Kincaid-Smith and Barlow[1] may be related to the presence or absence of myocardial damage, as will be discussed below.

Apparent conflicts and discrepancies in studies using nitrite compounds have been known and these complicated facts are interpreted as a result of their various responses and modes of action depending on the method of administration, species differences (human being or animal), and also functional status of the coronary arteries (physiological or atherosclerotic arteries).[1-25] In addition, many investigators do not agree as to the mechanism by which nitrites relieve angina or paradoxically precipitate or aggravate an acute stage of myocardial infarction. More recent works, however, seem to indicate that coronary flow is either diminished or unchanged by nitrites and attribute the relief of pain to reduced cardiac work and increased oxygen requirement.[illegible] From these observations and our present results, it would seem that the difference in behavior of the postinhalation diastolic sounds between the subjects with and without ischemic heart disease may be explained by the presence or absence of coronary artery disease or myocardial disease.

The PCW pressure decreased after amyl nitrite inhalation in 5 hypertensive patients, and all of these showed a diminution in the postinhalation diastolic sounds, suggesting that the decrease in these sounds was related to a drop in the left atrial pressure or left ventricular filling pressure, as reported by others.[1-29] Even though in our study intracardiac pressure measurements were not done in patients with ischemic heart disease showing intensification of the diastolic sounds during the test, this particular phenomenon might be associated with an elevation of left atrial pressure as a result of an increased flow load as described above and elsewhere.[illegible]

Despite the fact that the nitrites are well known to produce pain relief even in those patients with gallop rhythms or prominent atrial waves in the kinetocardiogram,[illegible] they are not always beneficial depending upon the mode of administration, dosage, or individual condition.[illegible]

As observed in this study, amyl nitrite may intensify the third and atrial sounds in patients who already have a handicapped myocardium due to ischemic heart disease, and thus the drug might be harmful in this group. The present study also suggests that amyl nitrite should not be given in too large a dose or too rapidly.

From the diagnostic point of view, however, the amyl nitrite inhalation test with special attention to the third and atrial heart sounds, represents a simple and useful procedure for evaluation of myocardial reserve function. The procedure itself may also be safer and more widely applicable than the exercise test, which may be contraindicated in patients with effort angina.

The direct writing phonocardiogram used for the study was satisfactory for recording the low-frequency vibrations such as the diastolic heart sounds.

Summary

1. Twenty patients with ischemic heart disease (Group A), 32 with diastolic hypertension (Group B), and 54 normal subjects (Group C) were studied in order to observe the effects of amyl nitrite inhalation on the third and atrial heart sounds.

2. Fifty-five per cent of Group A, [illegible] per cent of Group [illegible], and 4 per cent of Group C had a significant amplitude increase of these sounds following inhalation of amyl nitrite.

3. It is possible that an increased flow load to the impaired myocardium secondary to a rise in cardiac output and venous return after amyl nitrite inhalation is sufficient to account for the augmentation of the diastolic heart sounds in the majority of the patients in Group A.

4. An initial sudden drop in blood pressure and increase in heart rate may also

be responsible for intensification of the diastolic sounds resulting from further coronary insufficiency in the patients with ischemic heart disease

5 The amyl nitrite inhalation test with special reference to the diastolic heart sounds, is considered to be a simple and useful clinical procedure for evaluation of myocardial reserve function

REFERENCES

1 Sawayama, T Niki, I., Mitsuura, T and Ichinose, S. Exercise phonocardiogram Significance of the third and atrial sounds, Jap. Circ. J 30 1153 1966
2. Connolly D C., Kirklin, J W and Wood E. H : The relationship between pulmonary artery wedge pressure and left atrial pressure in man, Circulation Res. 2:434 1954
3 Gorlin, R Lewis, B. M Haynes, F W Spiegl, R. J and Dexter L. Factors regulating pulmonary capillary pressure in mitral stenosis IV Am. Heart J 41:834 1951
4. Daddario, R. C and Freis, E. D Kinetocardiogram, phonocardiogram and arterial pulse waves during acute hemodynamic changes, *Circulation* 34:423 1966.
5. Kerr A. J Manitsas, G T and Benenghini, I Effect of drugs on heart sound intensity J Maine M A. 57:278, 1966.
6. Deleon, A C., J and Perloff J K. The pulmonary hemodynamic effects of amyl nitrite in normal man, Am. Heart J 72:278 1966.
7 Johanovska, K., and Tomasek, R. Polygraphic study of hemodynamic changes after inhalation of amyl nitrite, Acta Univ Carol Med. 11 137 1965.
8. Perloff J K Calvin, J Deleon, A. C and Bowen, P Systemic hemodynamic effects of amyl nitrite in normal man, Am. Heart J 66:460, 1963.
9 Beck, W Schrire V Vogelpoel, L., Nellen, M and Swanepoel, A. Hemodynamic effects of amyl nitrite and phenylephrine on the normal human circulation and their relation to changes in cardiac murmurs, Am. J Cardiol. 8:341 1961
10. Mason, D T and Braunwald, E. The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm, Circulation 32 755, 1965.
11 Parry E. and Mounsey P Gallop sounds in hypertension and myocardial ischemia modified by respiration and other manoeuvers Brit. Heart J 23:393 1961
12 Kontos, H A., Shapiro, W and Kemp, V E. Observations on the atrial sound in hypertension Circulation 28:877 1963
13 Harris, W S., Rodin, P and Tchatznik, B Modification of the atrial sound by the cold pressor test, carotid sinus massage and Valsalva maneuver Circulation 28 1128, 1963
14 Sakamoto, T Kaito, G and Ueda, H. Electrocardiographic and phonocardiographic studies in hypertension. Part II Phonocardiographic study with special reference to the atrial sound and "Q-I" interval Jap. Heart J 1:213 1960.
15 Contro, S., Haring O M and Goldstein, W : Paradoxic action of amyl nitrite in coronary patients, Circulation 6:250, 1952.
16. Kincaid-Smith, P and Barlow J Atrial sound in hypertension and ischemic heart disease. With reference to its timing and mode of production, Brit. Heart J 1:479 1959
17 Gorlin, R., Brachfeld, N Macleod, C., and Bopp P Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work, Circulation 19 705 1959
18. Wegria, R Nickerson, J L Case, R. B and Holland, J F Effect of nitroglycerin on the cardiovascular system of normal person, Am J Med 10:414 1951
19 Fam W M and McGregor M Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia, Circulation Res. 15:355, 1964
20. Brachfeld, N Coronary vasomotor response to pharmacologic agents, Am. J Cardiol. 13 1 1964.
21 Honig C R., Tenney, S. M and Gabel, P V The mechanism of cardiovascular action of nitroglycerin. An example of integrated response during the unsteady state, Am. J Med. 29:910, 1960.
22. Fleck, S. Antianginal drugs Part II Human pharmacology of nitroglycerin, Am. Heart J 71:417 1966.
23 Brachfeld, N Bozer J L and Gorlin, R. Action of nitroglycerin on the coronary circulation on normal and mild cardiac subjects, Circulation 19:697 1959
24 Christensson, B Karlefors, T and Westling H Hemodynamic effects of nitroglycerin in patients with coronary heart disease, Brit. Heart J 27:511 1965
25 Bing, R J Bennish, A Bluemchen, G Cohen, A. Gallagher J P and Zaleski, E. J The determination of coronary flow equivalent with coincidence counting technic, Circulation 29:833, 1964
26. Hollander W Madoff I M and Chobanian, A. V Local myocardial blood flow as indicated by the disappearance of NaI[131] from the heart muscle Studies at rest, during exercise and following nitrite administration J Pharmacol. & Exper Therap. 139:53 1963
27 Bernstein, L., Friesinger G C Lichtlen, P R and Ross, R S Effect of nitroglycerin on myocardial blood flow in man as measured with Xenon[133] Circulation (Suppl. 3) 30:47 1964 (abstr)
28 Rowe, G. G Chelius C J Afonso, S Gurtner H P and Crumpton C. W Systemic and coronary hemodynamic effects of erythrol tetranitrate, J Clin Invest. 40 1217 1961
29 Johnson, J B Gross, J F and Hale, E. Effects of sublingual nitroglycerin on pulmonary artery pressure in patients with failure of the left ventricle, New England J Med. 257 1114 1957

30. Skinner, N. S., Leibeskind, R. S., Phillips, H. L., and Harrison, T. R.: Angina pectoris. Effects of exertion and of nitrites on precordial movements, AM. HEART J. 61:250, 1961.
31. Skinner, N. S.: Kinetocardiographic findings in patients with congestive heart failure and changes after therapeutic digitalization, AM. HEART J. 61:445, 1961.
32. Skinner, N. S., Nickerson, J. F., and Ingram, R. H.: Kinetocardiographic alterations in patients with congestive heart failure at rest and after exercise. The effect of digitalis, AM. HEART J. 61:458, 1961.
33. Fleming, J., and Hamer, J.: Effect of propranolol on left atrial systole in ischemic and hypertensive heart disease, Brit. Heart J. 29:257, 1967.
34. Sawayama, T., Shiozu, N., Niki, I., Mitsutura, T., and Ichinose, S.: Unusual form of impending myocardial infarction in a premenopausal woman, Jap. Circ. J. 29:943, 1965.
35. Wilkins, R. W., Haynes, F. W., and Weiss, S.: The role of the venous system in circulatory collapse induced by sodium nitrite, J. Clin. Invest. 16:85, 1937.
36. Proger, S. H., and Ayman, D.: Harmful effects of nitroglycerin. With special reference to coronary thrombosis, Am. J. M. Sc. 184:480, 1932.
37. Weiss, S., Wilkins, R. W., and Haynes, F. W.: Nature of circulatory collapse induced by sodium nitrite, J. Clin. Invest. 16:73, 1937.
38. Sprague, H. B., and White, P. D.: Nitroglycerin collapse—potential danger in therapy: Report of three cases, M. Clin. North America 16:895, 1933.
39. Leuth, H. C., and Hanks, T. G.: Unusual reactions of patients with hypertension to glyceryl trinitrate, Arch. Int. Med. 62:97, 1938.
40. Segall, N. H.: Drugs for anginal pain, Canad. M. A. J. 90:491, 1961.
41. White, P. D.: The significance and treatment of cardiac symptoms, New England J. Med. 205:907, 1931.
42. Master, A. M., Jaffe, H. L., and Dack, S.: The drug treatment of angina pectoris due to coronary artery disease, Am. J. M. Sc. 197:774, 1939.

Malformations of the aortic valve in patients with the tetralogy of Fallot

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Right-sided aortic arch, bicuspid or absent pulmonic valve, atrial septal defect, persistent left superior vena cava, and pulmonary arterial branch stenosis are malformations frequently associated with Fallot's tetralogy.[1,2] Abnormalities of the aortic valve, however, are rare. The findings in a recent patient with aortic regurgitation associated with right ventricular outflow obstruction and ventricular septal defect stimulated us to examine the aortic valves of other patients with tetralogy of Fallot studied by us at necropsy.

Patients studied

The hearts were examined in 45 patients (25 males) who had large ventricular septal defects, right ventricular outflow obstruction, and dextroposition of the aorta. In 7 patients there was pulmonic atresia, while in 38 outflow obstruction resulted from infundibular and/or pulmonic valvular stenosis. Resting systemic arterial oxygen saturation had been 90 per cent or above (acyanotic tetralogy) in 5 patients and ranged from 32 to 88 per cent in the other 40 subjects. The ages of the 45 patients ranged from 7 weeks to 48 years (average = 11 years) and 9 were older than 20 years.

Results

Five of the 45 patients with tetralogy proved to have anatomic malformations of the aortic valve (Table I). All 5 were severely cyanotic and 4 of them were adults. Abnormalities on physical and roentgenographic examinations and significant hemodynamic alterations resulted from the aortic valvular lesions in 2 patients (Table I, Patients 1 and 2, Figs. 1 and 2), and death in Patient 2, described in detail elsewhere, was related to unsuccessful aortic valvulotomy. In Patient 3 (Fig. 3) fibrous fusion of 1 of 3 commissures of an otherwise normal aortic valve produced a small (7 mm. Hg) systolic pressure gradient. No clinical or hemodynamic abnormalities could be attributed to the aortic valvular abnormalities in Patients 4 and 5.

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Table I Clinical and anatomic data in 5 patients with malformations of the aortic valve and Fallot's tetralogy

Patient No.	Age	Sex	Pathoanatomic features of aortic valvular lesion	Clinical findings attributed to aortic valvular lesion	Other cardiovascular abnormalities	Comment
1	22	F	Congenitally bicuspid. Wide separation of cusps at one commissure	Aortic regurgitation murmur 125 mm Hg femoral arterial pulse pressure left ventricular enlargement, dilated ascending aorta, moderately severe aortic regurgitation by aortogram	Congenitally bicuspid pulmonic valve	Late (7 years) thrombosis of Blalock Taussig anastomosis. Died 5 days after emergency closed, pulmonic valvulotomy
2	45	F	Heavily calcified, stenotic 3-cuspid	Left ventricular enlargement, calcified aortic valve 70 mm Hg right ventricular to brachial arterial peak systolic pressure gradient	Focal fibrous thickening of mitral and tricuspid valves	Acute rheumatic fever at ages 4, 7 and 12 yrs. Died 3 hours after Blalock Taussig anastomosis and closed aortic valvulotomy
3	30	M	Fibrous fusion at commissure between posterior and left anterior cusps	7 mm Hg right ventricular to brachial arterial peak systolic pressure gradient	Accessory orifice tricuspid valve (in septal leaflet)	Died of gastrointestinal hemorrhage, acute renal failure and septicemia 7 weeks after complete repair of tetralogy
4	35	F	Partial fibrous fusion at commissure between posterior and right anterior cusps	None	Ventricular septal insertion of chordae tendineae from anterior mitral leaflet. Valvular incompetent patent foramen ovale	Died following Blalock Taussig anastomosis
5	11	F	Verrucal endocarditis	None	Verrucal endocarditis of tricuspid and pulmonic valves. Valvular incompetent patent foramen ovale	Died of left ventricular failure 12 hours after complete correction of tetralogy

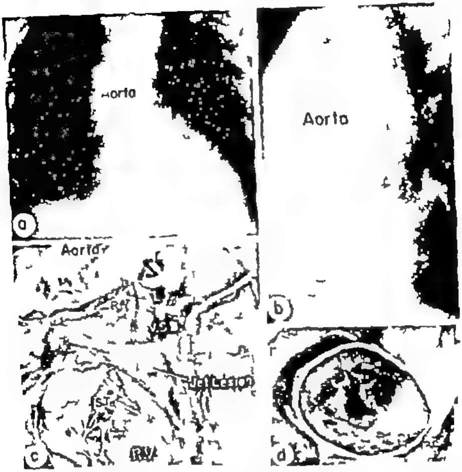

Fig. 1. Patient 1. Anteroposterior, a, and lateral, b, chest roentgenograms following injection of contrast material into the aortic root. The ascending aorta is dilated and contrast material refluxes into the ventricles, predominantly the right one. c, Opened right ventricle (R.V.) and congenitally bicuspid aortic valve, which has right (R.) and left (L.) cusps. The aortic valve overrides the ventricular septal defect (V.S.D.) and a jet lesion is present on the endocardium of the right side of the septum. Sticks have been placed in the coronary arterial ostia. S.T. Septal tricuspid leaflet. d, Intact aortic valve from above. The 2 cusps are widely separated and focally thickened at the anterior commissure.

Comments

Bicuspid aortic valves in patients with Fallot's tetralogy have been reported twice previously,[2] but apparently the valves were competent. Aortic regurgitation in Patient 1 was produced by the wide separation of the 2 cusps at the anterior commissure. In 3 previously reported patients with tetralogy of Fallot,[3] aortic regurgitation was ascribed to prolapse of an aortic valvular cusp. Aortic regurgitation occasionally occurs in patients with isolated ventricular septal defect, and since the overriding aortic valvular cusps in patients with Fallot's tetralogy appear to be even less well supported, it is surprising that aortic regurgitation occurs so infrequently in them. Edwards and associates[4] illustrated the heart of an adult patient with aortic regurgitation and Fallot's tetralogy.

The etiology of the aortic stenosis in Patient 2 is uncertain, but it probably was rheumatic in origin. Other patients with Fallot's tetralogy and rheumatic aortic valvular disease have not been described. The cause of the fusion of the one commissure in Patient 3 is unknown. A morphologically identical aortic valve in a patient with Fallot's tetralogy also has been il-

lustrated by Edwards and associates.[6] In Patient 4 partial fusion of the leaflets and focal fibrous thickening of the adjacent posterior aortic valvular cusp appears to have resulted from turbulent blood flow and endocardial jet lesions were also found on the upper margin of the ventricular septum and on the anterior right ventricular wall

Although infective endocarditis occurs commonly in patients with tetralogy of Fallot[7] noninfective thrombotic endocarditis has not been reported in these subjects. No organisms were observed histologically in the valvular vegetations of Patient 5 but she had recently received penicillin and streptomycin

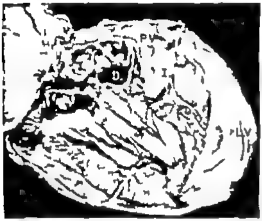

Fig. 2. Patient 2. Opened hypertrophied right ventricle (*R.V.*), stenotic infundibular (*I*) inlet (dashed arrow), and stenotic pulmonic (*P.V.*) and aortic valves The aortic valve which overrides the ventricular septal defect (*D*), consists of 3 heavily calcified, immobile cusps. The circumference of the aortic root is designated by the black dotted line. The left ventricle (*L.V.*) is also hypertrophied

Summary

Anatomic malformations of the aortic valve were observed in 5 of 45 patients with the tetralogy of Fallot studied at necropsy In one, the valve was congenitally bicuspid and incompetent. A second had probable rheumatic aortic stenosis. Clinically insignificant fusion of 2 aortic valvular cusps was found in each of 2 patients, and a fifth had vegetative endocarditis without organisms. Aortic valvular lesions in patients with Fallot's tetralogy have been described only rarely in the past.

REFERENCES

1. Lev M and Eckner F. A. O.: The pathologic anatomy of tetralogy of Fallot and its variations, Dis. Chest 45:251 1964
2. Nagao, G. I. Daoud, G. I. McAdams, A. J. Schwartz, D. C. and Kaplan, S. Cardiovascular anomalies associated with tetralogy of Fallot, Am J Cardiol. 20:206, 1967
3. Collins, N P Morrow A. G and Braunwald, E. Tetralogy of Fallot with rheumatic stenosis of the aortic valve, Am. Heart J 60:624, 1960.
4. Bahnson, H. T Spencer F C., Landtman, B. Wolf, M D Neill, C. A., and Taussig H. B. Surgical treatment and follow-up of 147 cases of

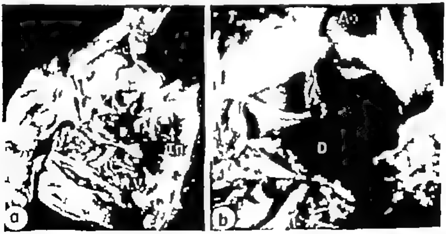

Fig. 3 Patient 3 *a* opened hypertrophied right ventricle (*R.V.*), aortic valve and ascending aorta (*Ao.*). *Inf.*, right ventricular infundibulum. *b* closer view of the aortic valve, which overrides the septal defect (*D*), showing fibrous fusion of the posterior and left anterior cusps.

tetralogy of Fallot treated by correction, J Thoracic & Cardiovas. Surg 44:419 1962.
5. Edwards, J E., Carey L. S., Neufeld, H. N and Lester R. G. Congenital heart disease Correlation of pathologic anatomy and angiocardiography Philadelphia, 1965 W B. Saunders Company p. 421
6. Edwards, J E. Carey L. S., Neufeld, H. N and Lester R. G. Congenital heart disease Correlation of pathologic anatomy nd angiocardiography Philadelphia, 1965 W B. Saunders Company p. 402.
7 Nadas, A. S. Pediatric cardiology ed. 2, Philadelphia, 1963, W B Saunders Company p. 215

Physical characteristics and exercise performance of pedicab and upper socioeconomic classes of middle-aged Chinese men

A comparative study of some risk factors for coronary heart disease

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An inverse relationship between habitual physical activity and proneness for ischemic or coronary heart disease has been suggested, but not clearly established by studies of bus drivers and conductors, postoffice workers, and railroad employees. Socioeconomic status may be an important determinant of risk factors for coronary disease when such status, for example, permits dietary excesses and a sedentary way of life.[1-4] Just as epidemiological surveys of populations at a high risk are valuable, similar surveys of populations at a low risk may be informative if the rare cases among markedly different groups are identified and characterized. A previously reported pilot study of middle-aged Chinese men in Taiwan described an unusually low prevalence of coronary heart disease in that population.[5] It also demonstrated the feasibility of identifying individuals with myocardial ischemia after maximal exertion by transient S-T segment depression in the electrocardiogram (ECG). Furthermore, the age-specific prevalences of S-T segment depression of 1 mm. or more were less in Chinese men, who were also characterized by significantly lower cholesterol concentrations than observed in American men of comparable age.[6] Accordingly, further study of 2 groups of middle-aged Chinese men was designed. A low socioeconomic group of self-selected pedicabmen was chosen since their daily arduous physical exertion and restricted diet imposed by meager earnings approached the ultimate in minimizing risk factors for coronary disease. A larger group of volunteers from the upper socioeconomic classes provided

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a comparison group of identical race and geographical environment with similar age distribution.

The purpose of this study is to test a hypothesis in a population selected for low incidence of coronary heart disease. The hypothesis states that enhanced physical activity and restricted diet, imposed by a low socioeconomic status would prevent or delay the usual increment in age specific prevalence of postexertional S-T segment depression in middle-aged men. This sign of transient myocardial ischemia after maximal exertion is selected as the earliest detectable evidence of coronary heart disease in healthy individuals.

Materials and methods

A total of 102 self-selected Chinese pedicabmen in Taipei City aged 40 to 59 years, responded to our request and volunteered for the proposed study An initial screening examination for overt disease excluded 2 from a treadmill exercise test. One was excluded because of severe hypertension the other because of left ventricular hypertrophy and strain in the resting ECG The remaining 100 had been doing this work for an average of 11 years, ranging from 3½ to 25 years. (A pedicab [Fig 1] is a tricyclic vehicle which transports 1 or 2 passengers who sit on the back seat it is manually powered by the pedicabman who pedals in front) The pedicabmen bicycle about 4 hours, for an average distance of 40 kilometers, daily Their average daily income is 70 New Taiwan dollars (U.S. $1 75) For their loss of time at work to participate in this study they were paid 50 New Taiwan dollars.

The control group for the purposes of this study consisted of 1,346 senior bank or power company employees of managerial class, and military officers of the rank of colonel and above who resided in Taipei City

All were studied by the same methods employed in the Taiwan Cardiovascular Study [3,9,1] A detailed medical history and physical examination were obtained by the examining physician. Anthropometric measurements hematocrit urinalysis, fasting blood sugar serum cholesterol and uric acid first second of forced expiratory volume and vital capacity were determined. A standard chest x-ray film was obtained for the transverse diameters of the chest and the heart (which were measured by a radiologist) A 12-lead resting ECG was recorded and coded by Minnesota criteria.[11] This tracing and the clinical data were reviewed by an examining cardiologist to exclude individuals who should not be exercised according to criteria described elsewhere [12] Maximal exercise performance was assessed with a multistage treadmill test with continuous electrocardiographic monitoring with a single bipolar precordial lead [13,1] Each participant was encouraged to continue walking on the treadmill without handrail support, until he felt exhausted definite chest pain occurred or electrocardiographic

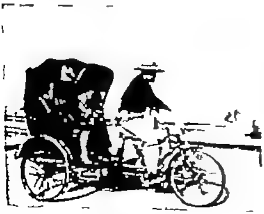

Fig. 1 Pedicab with occupants.

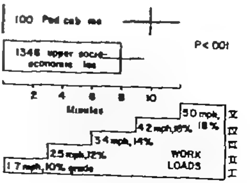

Fig. 2 Duration of maximal exercise for 100 pedicabmen and 1,346 men of upper socioeconomic class (means ± standard deviation).

signs of severe arrhythmias were observed. The exercise was graded in speed and level into a maximum of 7 stages (Fig. 2). At the end of maximal exertion the treadmill was slowed to 1 m.p.h. and the subject walked on the level for 2 minutes to avoid postexertional dizziness due to venous pooling in the legs.[8] Following this, each sat in a chair for another 4 minutes while ECG monitoring continued. ECG tracings were recorded at each submaximal stage, at maximal exercise, and each minute after maximal exercise for 6 minutes. Blood pressure was measured with a clinical sphygmomanometer before exercise, immediately after maximal exercise, and 3 and 6 minutes after exercise.

Results

Physical characteristics. Mean values for several physical characteristics of the pedicabmen and the men in the upper socioeconomic class are presented in Table I. The pedicabmen were of equivalent age and height as the other group, yet body weight, all measurements of skinfolds, both arm and waist circumferences, as well as vital capacity and transverse chest diameter were significantly less in the pedicabmen. Concentrations of serum cholesterol and uric acid were also significantly lower in the pedicabmen.

The only variable which was significantly greater in the pedicabmen was the transverse diameter of the heart. In relation to the smaller dimensions of the chest and lower vital capacity, the cardiothoracic ratio was significantly higher. Despite this, blood pressure was not increased. The resting heart rate was significantly lower, consistent with a slightly larger heart volume, and possibly a larger stroke volume.

Electrocardiographic items. There were several salient differences in the frequency of electrocardiographic items classified according to the Minnesota code (Table II). High amplitude R waves in the resting ECG were noted in 28 per cent of the pedicabmen and only 1.6 per cent of the men in the upper socioeconomic class. Sinus bradycardia and isolated premature beats were more common in the pedicabmen. Conversely, the prevalences of left axis deviation (−30 degrees or more), right axis deviation (+ 90 degrees or more), both J and S-T segment depressions and

Table I. Physical characteristics (means ± standard deviations)

	100 Pedicabmen	1,346 Upper socioeconomic men	Significance test (DF = 1,444)	
			t	*p*
Age (yrs.)	46.7 ± 5.0	47.1 ± 4.6	0.8	
Height (cm.)	167 ± 5.0	168 ± 2.[illegible]	1.8	
Weight (Kg.)	59.3 ± 8.6	62.5 ± 9.2	3.2	< 0.01
Triceps skinfolds (cm.)	0.8 ± 0.4	1.4 ± 0.6	9.7	< 0.001
Scapular skinfold (cm.)	1.1 ± 0.6	1.8 ± 0.8	8.0	< 0.001
Abdominal skinfold (cm.)	1.0 ± 0.6	1.5 ± 0.6	8.2	< 0.001
Arm circumference (cm.)	[illegible].7 ± 2.5	27.6 ± 2.7	6.8	< 0.001
Waist circumference (cm.)	73.4 ± 7.4	77.9 ± 8.2	5.2	< 0.001
Hematocrit (%)	42.2 ± 2.9	41.6 ± 3.3	1.8	
Fasting blood glucose (mg. %)	93 ± 11	92 ± 12	1.2	
Cholesterol	179 ± 30	198 ± 35	5.4	< 0.001
Uric acid	3.3 ± 0.5	3.8 ± 0.6	7.9	< 0.001
1 second expiratory flow (L.)	2.3 ± 0.5	2.4 ± 0.5	1.8	
Vital capacity	3.2 ± 0.7	3.3 ± 0.6	2.7	< 0.01
Heart diameter (trans.) (cm.)	12.5 ± 1.2	12.1 ± 1.3	3.2	< 0.01
Chest diameter (trans.) (cm.)	27.4 ± 1.7	28.7 ± 2.0	6.6	< 0.001
Cardiothoracic ratio	0.46 ± 0.04	0.42 ± 0.04	8.1	< 0.001
Systolic blood pressure (mm. Hg)	118 ± [illegible]	120 ± [illegible]	1.1	
Diastolic blood pressure (mm. Hg)	76 ± 9	76 ± 12	0.0	

particularly sinus tachycardia were more common in the upper socioeconomic class of men.

Exercise performance. The frequency of symptoms, number of exercise stages completed and means of several exercise variables are listed in Table III. Whereas, the occurrence of fatigue with this multi stage test of maximal exertion was equal in both groups of men pedicabmen more frequently complained of dizziness. Dyspnea was more often noted by men in the upper socioeconomic class.

Maximal heart rate was equivalent, 170 to 172 per minute in the 2 groups of men (Fig 3). Duration of effort to achieve this limit was significantly 2 minutes longer in the pedicabmen ($p \leq 0.001$) [Fig 2]. Of interest 21 per cent of these men completed Stage IV and 1 per cent, Stage V in contrast to only 4 per cent of the men in the upper socioeconomic class who completed Stage IV. Maximal systolic blood pressure was slightly higher in the pedicabmen yet there was no difference in diastolic pressures between the 2 groups of men. However pulse pressure at maximal exercise was significantly greater in the pedicabmen than in men of the upper socioeconomic class (Table III).

The rate of recovery was faster in the pedicabmen. Mean heart rate was 12 beats lower at 3 minutes, and 8 beats lower at 6 minutes after maximal exertion. These

Table II *Minnesota coding of electrocardiographic items*

	Pedicabmen (N = 100)	Upper socioeconomic men (N = 1,344)	(%)
Resting ECG items			
Q pattern	0	1	(0.1)*
QRS deviation			
LAD	1	49	(3.6)
RAD	0	27	(2.0)
High amplitude R			
LVH	28	22	(1.6)†
RVH	0	5	(0.4)
S-T segment			
J ≥ 1 mm.	0	12	(0.9)
J 0.5 to 0.9 mm.	0	20	(1.5)
S-T ≥ 1 mm.	0	1	(0.1)
S-T 0.5 to 0.9 mm.	0	[illegible]	(1.2)
T abnormalities			
Amplitude −1 to −5 mm.	0	4	(0.3)
Flat or diphasic	0	36	(2.7)
AV conduction, 1 A-V block	0	2	(0.2)
Ventricular conduction			
RBBB	1	14	(1)
Incomplete	2	34	(2.5)
Arrhythmias			
Frequent premature beats	3	17	(1.2)
Sinus tachycardia	0	54	(4.0)
Sinus bradycardia	10	28	(2.0)
Postexercise (maximal) ECG items			
Respiratory variation S-T junction and segment	13	123	(9.1)
S-T segment 0.5 to 0.9 mm.	2	55	(4.1)
S-T segment ≥ 1 mm.	5	94	(7.0)
T inversion	1	13	(1.0)
Diphasic or flat T	3	94	(7.0)
Arrhythmias	5	53	(4.1)

*1 item: D = 0.04 sec. or more. Q/R = 1/3 or more.
†χ^2 test = 172, $p < 0.0001$.

Table III Exercise performance (means ± standard deviation)

	100 Pedicabmen	1,346 Upper socio-economic men	Significance test (DF = 1 444) t	Significance test (DF = 1 444) p
Heart rate				
Rest	70 ± 9	79 ± 12	7 0	< 0 001
Maximal	170 ± 18	172 ± 16	1 4	
3 min recovery	108 ± 15	120 ± 17	6 9	< 0 001
6 min recovery	99 ± 12	107 ± 15	5 7	< 0 001
Systolic pressure				
Rest	123 ± 15	127 ± 18	2 0	< 0 05
Maximal	178 ± 25	170 ± 28	2 9	< 0 05
3 min. recovery	144 ± 21	147 ± 22	1 1	
6 min. recovery	124 ± 16	128 ± 19	2 0	< 0 05
Diastolic pressure				
Rest	79 ± 8	80 ± 11	1 5	
Maximal	75 ± 12	75 ± 15	0 1	
3 min recovery	75 ± 9	76 ± 12	0 5	
6 min recovery	78 ± 9	78 ± 12	0 2	
Pulse pressure				
Rest	46 ± 12	46 ± 13	1 0	
Maximal	103 ± 27	94 ± 26	3 5	< 0 001
3 min recovery	69 ± 21	71 ± 22	2 6	< 0 05
6 min recovery	42 ± 10	43 ± 11	1 3	
Duration (sec.)	606 ± 112	481 ± 90	13 1	< 0 001
Exercise stages completed (%)				
II	100	89		
III	77	27		
IV	21	4		
V	1	0		
Prevalence of symptoms (%)				
Fatigue	84	85		
Dyspnea	21	31		
Dizziness	28	12		
Chest pain	2	1		
Claudication	1	0.2		

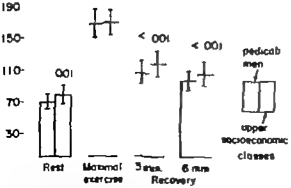

Fig 3 Heart rate responses at rest, at maximal exertion, and at 3 and 6 minutes of recovery for 100 pedicabmen and 1,346 men of upper socioeconomic class (means ± standard deviation).

differences paralleled the 9 beats per minute lower heart rate at rest. Accordingly the change in heart rate from rest to maximal exertion was actually greater in the pedicabmen than in the upper socioeconomic class of men. This might suggest either greater vagal inhibition or less sympathetic stimulation of the sinus pacemaker in the presence of slightly larger heart volumes. Although systolic blood pressures were slightly lower ($p < 0.05$) in the pedicabmen at 3 out of 4 periods of observation there were no differences in diastolic blood pressure

Electrocardiographic responses to maximal exercise The only significant ECG change

Table IV *Age specific prevalence of S-T segment depression* ≤ -0.1 *mv after maximal exercise*

Age groups (yrs.)	*Pedicabmen*		*Upper socioeconomic men*		
40 to 44	2/40	5.0%	15/462	3.2	
45 to 49	1/32	3.1%	28/456	6.1	
50 to 54	1/21	4.7%	38/354	10.7	
55 to 59	1/7	14.3%	13/74	17.5%	
40-49	3/72	4.1	43/918	4.7	$\chi^2 = 24.6$
50-59	/28	7.1	51/428	11.9%	$p < 0.0001$

NS (pedicabmen 40-49 vs. 50-59); NS (40-49, pedicabmen vs. upper socioeconomic men); NS (50-59, pedicabmen vs. upper socioeconomic men)

other than acceleration in heart rate observed as a result of maximal exercise was S-T segment depression of 1 or more millimeters. The frequencies of this response for the 2 groups of men are listed in Table IV. There were no significant differences in prevalence of this response between the 2 classes of men. Within the upper socioeconomic class of men however there was a highly significant increment in the age specific prevalence, when the frequencies for the larger number of men in the 2 decades were compared. The over-all prevalence of this response in all 1,446 men was 6.8 per cent.

Discussion

Chinese pedicabmen constitute an occupational group which is characterized by repetitive endurance type of rhythmical muscular exercise every day for many years. Concomitantly their low socioeconomic status, as determined by a very modest earning capacity restricts them from dietary overindulgence, both qualitatively and quantitatively. The pedicabmen are particularly suited to test the epidemiological hypothesis that regular physical exertion and dietary restriction for years may alter either the prevalence or the magnitude of risk factors currently associated with the pathogenesis of ischemic heart disease due to coronary atherosclerosis in Western countries. An appropriate test of this hypothesis must utilize another group of men of the same race, comparable age distribution and general environment who are observed concurrently. For this purpose the larger group of controls were selected from senior employees and managers of banks and the power company as well as senior military officers also residing in Taipei for several years. The documentation of their epidemiological characteristics will be reported separately,[16] but the measurements cited here clearly indicate pertinent differences in relation to the pedicabmen. Such differences for men of identical race comparable age and same geographical residence almost certainly result from less restricted dietary habits and more sedentary occupational habits. Both major groups of men were selected after initial screening examination, to exclude any with clinically overt cardiovascular disease. Any observed differences in risk factors exercise performance, or postexertional electrocardiographic manifestations of transient myocardial ischemia relate to healthy middle-aged men, rather than clinical cases. Furthermore, the appraisal of the hypothesis is constrained by selection of a population sample which is known to experience clinical manifestations of coronary heart disease such as angina pectoris, myocardial infarction or sudden death, quite infrequently.[1,16,17]

Examination of the 100 pedicabmen revealed significantly lower mean values for body weight, subcutaneous fat as measured by skinfolds at 3 selected sites serum cholesterol and uric acid and vital capacity The cholesterol mean of 179 mg per cent compared favorably with the mean of 178 mg per cent reported by Tsai and associates for healthy Chinese, and a mean of 173 in a previous study of a low socioeconomic group (enlisted men in the Chinese army)

While it is probable that diet is a major determinant of cholesterol concentration other factors such as genetic predisposition and physical activity exert an influence Many investigators have observed that endurance type of physical training may affect body weight, adiposity and serum lipids. Skinner and colleagues studied the effect of a 6-month endurance exercise program on middle aged men and found a significant increase in exercise capacity and body specific gravity accompanied by a decrease of body fat and serum lipids. Hoffman and co-workers observed the effect of exercise among senior air officers who showed lower levels of serum lipids than a physically inactive control group Hernberg observed that middle aged men with a higher physical work capacity have lower serum cholesterol concentrations. Similar effects of physical training on serum lipids have been observed by Golding and Rochelle Montoye and associates found the serum total cholesterol concentration and uric acid were significantly higher in a group of business executives than general population and high serum cholesterol appeared to be associated with less physical activity

Radiographic examination of the chest demonstrated slight, but significant enlargement of the silhouette in the pedicabmen. Similar enlargement was reported in 23 out of 46 Chinese ricksha pullers who were studied by Tung and co-workers in 1934 The average age of these pullers was 33 years, and the duration of their occupation averaged 8 years. None of them had elevated blood pressures at rest while 7 had systolic murmurs. The cardiac enlargement was considered to be physiologic hypertrophy In 2 men who changed their occupation it was reversible The authors concluded that the enlargement did not constitute nor predispose to cardiovascular disease Similar enlargement, averaging 12.9 cm has been observed in endurance athletes. Radiographic examination immediately after a marathon race of 26 miles showed a marked reduction of 2 cm. in heart size associated with the loss of fluids. It will be of interest to ascertain whether the heart size of the pedicabmen recedes when they change their occupation to a more sedentary one in the future. The Chinese government is already retraining similar men to become taxicab drivers. This will present an extraordinary opportunity to observe the chronic effects of restricted physical activity together with daily emotional stresses imposed by the congested traffic.

Electrocardiographic evidence of hypervoltage of R waves which is often attributed to left ventricular hypertrophy was present in 28 per cent of the pedicabmen. Yet none of them also showed the usual ST T changes of left ventricular strain. Of interest, however 19 per cent had cardiothoracic ratios by x ray examination greater than 0 5 High voltage of QRS and T waves is characteristic of ventricular enlargement in well trained athletes with no evidence of heart disease. Possibly the proximity of the left ventricle to the left precordial leads is another factor Exercise duration of pedicabmen was not correlated with heart size, however ($r = -0.02$ not significant) Neither was the prevalence of postexertional S-T segment depression greater in the pedicabmen with hypervoltage Similarly Beckner and Winsor found only 1 out of 165 younger athletes with an average age of 27.9 years showed this response to distance running. This was in contrast to the association of this ECG sign of myocardial ischemia reported for sedentary Chinese men tested in the same manner

Both pedicabmen and men in the upper socioeconomic class attained similar maximal heart rates (Table III) Heart rate accelerated more slowly in the pedicabmen since they had to exercise for 2 minutes longer on the average, and at an even higher work load to attain the comparable maximal heart rate. Also in accordance with better physical conditioning heart

rates decelerated more rapidly after exertion in the pedicabmen even though they attained a greater work load.

The prevalence of postexertional S-T segment depression of 1 mm or more (≤ -0.1 mv.) was *not* significantly less in the 28 pedicabmen of 50 to 59 years of age than observed in the 428 men in the upper socioeconomic class (Table IV). Despite a suggestion of the expected increasing tend in age-specific prevalence of this response, it was not established statistically for the pedicabmen. This possibility was tested further by additional data on 80 enlisted men in another low socioeconomic class (who were previously reported in the pilot study[6]). With increasing age from the range of 40 to 49 to that of 50 to 59 years, the age-specific prevalence was insignificantly increased in the small number of older men ($\chi^2 = 1.15$, not significant). Quite different results were found, however, for the large number of men in the upper socioeconomic class. In the latter group, the age-specific prevalence increased from 4.7 to 11.9 per cent for these 2 decades of age ($\chi^2 = 24.6$, $p < 0.0001$) (Table IV).

The inference is drawn that dietary restrictions and/or physical activity associated with the lower socioeconomic status of the pedicabmen permit both a greater exercise capacity and more appropriate rates of change in heart rate with exertion. Additionally, when continued for years they may protect against or delay the commonly observed rise in age-specific prevalence of postexertional ECG evidence of myocardial ischemia which is readily demonstrated in a much larger number of men of identical race, of 50 to 59 years of age, and similar general environmental status. One cannot be certain, however, that some older pedicabmen have not already discontinued their occupation because of cardiovascular symptoms with exertion.

Summary

1. A comparative study of physical characteristics and exercise performance of Chinese men of 40 to 59 years of age included 100 pedicabmen and 1,346 men from the upper socioeconomic class in Taipei, Taiwan. The daily arduous physical exertion and restricted diet imposed by meager earnings of the pedicabmen provided a group which approached the ultimate in minimizing risk factors for coronary heart disease.

2. The pedicabmen were of comparable age and height, yet significantly lower mean body weight, skinfolds, circumferences of arm and waist, and serum concentrations of cholesterol and uric acid were characteristic of greater physical conditioning and prolonged dietary restrictions. Heart size was slightly larger, while greater exercise capacity, delayed acceleration of exertional heart rate, and more rapid postexertional deceleration of heart rate documented physical conditioning of the cardiovascular system.

3. Whereas the usual trend for progressive increments in age-specific prevalence of S-T segment depression after maximal exertion was clearly demonstrated in men from the upper socioeconomic classes, the slight increase in a small number of older pedicabmen was not statistically significant. The protective role of dietary restrictions and/or enhanced physical activity imposed by a low socioeconomic status might be inferred from these observations.

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REFERENCES

1. Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G., and Parks, J. W.: Coronary heart disease and physical activity of work, Lancet 2: 1053, 1953.
2. Kahn, H. A.: The relationship of reported coronary heart disease and physical activity of work, Am. J. Publ. Health 53: 1058, 1963.
3. Taylor, H. L., Klepetar, E., Keys, A., Parlin, N., Blackburn, H., and Puchner, T.: Death rates among physically active and sedentary employees of the railroad industry, Am. J. Publ. Health 52: 1697, 1962.
4. Taylor, H. L.: Occupational factors in the study of coronary heart disease, International symposium on physical activity and cardiovascular health, Canad. M. A. J. 96: 825, 1967.
5. Epstein, F. H.: Epidemiological approach to the study of coronary heart disease, Medical Times 94: 1155, 1966.
6. Alexander, E. R., Ting, N., Grayston, J. T., Lu, C., Li, Y. B., and Bruce, R. A.: Pilot study of ischemic heart disease in Taiwan, Arch. Environ. Health 10: 689, 1965.
7. Dunn, A. E., Peterson, D. R., Blackmon, J. R.,

and Bruce R A Myocardial ischemia after maximal exercise in healthy man, Am. Heart J 69 11 1965
8 Doa A E Peterson D R Blackmon J R. nd Bruce R A. Myocardial ischemia after maximal exercise healthy men. One year follow-up of ph sically activ and inactive men, Am J Cardiol I 69 1966.
9 Bruce, R A Compar t ve prev lence of segme tal ST depression after maximal exercise in healthy men Seattle nd Taipei, Karvonen M T and Barr A J ed tor Physical ctivity nd the heart, Springfield Ill 1967 Ch les C Thom Publisher h p 11 p 144
10 Li, Y B Fng N Chiang, B N Alexander F R Bruce R A nd Gray ton J T Electrocardiographic esponse t maximal exercise T eadm ll nd double m ster exer ise test middle-aged Chinese men, Am J Cardiol. 20:541 1967
11 Blackbu H Keys A Simonson, E Rautaharj P nd P me S The electrocardiogram population tudy A classification system Circulation 21 1160 1960
12 Bruce, R A Kattus, A A nd Mazzarella, J A Report of the Comm ttee on Saf ty Procedures, Karvonen, M T and Barry A J editor Physical activity and the heart, Springfield, Ill 1967 Charles C Thomas, P blisher chap. 20, p 245
13 Bruce, R A Blackmon J R Jones, J W and Strait, G Exercising test ad lt normal subjects and cardiac patient Pediatrics 32 742 1963
14. Bruce, R A. Cardiovascular f nction test, Physical activity and the heart, Springfield, Ill. 1967 Charles C Thomas P blisher
15 Tung N and Alexander E R Unpubl shed observations, in preparation
16 Tsai, H C Yeu T S Che C M and Wu T L Cl ical observation on myocardial infarction in 1954 t 1959 hosp tal material J Formosan Med. Assoc 59:608, 1960.
17 Yeh S. Some geographic aspects of some common diseases Taiwan I Arteriosclerosis and collagen disease, I t. Path 6:81 1965
18 Tsai, H. C., Wu, C. C., and Chen J S. Cholesterol levels in patients with coronary atherosclerotic heart disease J Formosan Med Assoc. 61:1031 1962.
19 Sk nner J S. Holloszy J O Toro, G Barry A J and Cureton, T K Effect of ix-month program of endurance exercise I work tolerance, serum lipids and VLF-ballistocardiogram of fiftee middle-aged men n Karvonen, M T nd Barry A. J editors Physical activity and the heart Springfield 1967 Charles C Thomas, Publisher chap. 8, p. 79
20 Hoffman, A A N lson W R and Goss, F A. Effects of exercise program on plasma lipid of se ior air force officers, Am J Cardiol 20:516 1967
21 Hernberg S Correlation between phy ical working capacity and serum cholesterol in leading businessmen n Karvonen, M T and Barry A J ed tors Physical activity in the heart, Springfield Ill., 1967 Charles C Thomas, P blisher
22 Golding, L A Effect of physical training pon total serum cholesterol levels, Res. Quart. 32:499 1961
23 Rochelle, P H Blood plasma cholesterol changes during phy ical training program Res. Quart 32:538, 1961
24 Montoye, H J F ulkner J A Dodge, H J Mikkelson W M Willis, P W and Block, W D Serum uric acid among business executives— th observations on other coronary heart disease isk factors, Ann. I t. Med. 66:838 1967
25 Tung D L Hsieh, C K., Bien C W and Dieuaide, F R The heart of ricksha pullers, Am. Heart J 10 79 1934.
26. Beckner C L and Winsor T Cardiovascular ad ptations to prolonged physical effort Circulation 9:835 1954

Experimental and laboratory reports

Cardiovascular response to acute thermal stress (hot dry environment) in unacclimatized normal subjects

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Although the physiological responses to various environmental temperatures have been the subject of many reports in the past, controversy continues to exist regarding the role of cardiac output, oxygen consumption, and arteriovenous (A-V) oxygen differences in man's adaptation to acute heat stress. It has become increasingly evident that part of the discrepancy between conclusions has resulted from variations in the methodology used, the type of subjects tested, and the environmental conditions under which subjects were studied.

This paper reports on the hemodynamic responses obtained in 16 normal untrained male volunteer subjects who were studied at supine rest and exercise in a comfortable environment and at three different temperature levels. A comparison of measurements obtained in this manner should provide a clearer and more valid insight into the hemodynamic changes which occur during acute heat stress. Furthermore, the proposed study was undertaken in order to establish a norm by which the circulatory adjustments of subjects with cardiovascular diseases exposed to hot dry environments may be compared. Concerning this latter subject, there is a relative paucity of information.

Methods

Studies on 16 normal unacclimatized male volunteer subjects, ages 22 to 41 (average age 27 years) form the basis of this report. Subjects were admitted to the hospital prior to the study and were judged to be in good health following a careful history, physical examination, and routine laboratory studies including chest x-ray and resting electrocardiogram. The volunteers were familiarized with the study by participating in a practice run of the entire procedure one time prior to the morning of the study. All measurements were made in the postabsorptive, nonsedated state. All 16 subjects were studied in a climatic chamber at a comfortable environment and following 1 to 1½ hours of exposure to

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a hot dry climate. Five subjects were studied at 78° and 100° F, six subjects at 78° and 115° F, and five subjects at 78° and 125° F. Relative humidity (R.H.) was held constant at approximately 42 per cent for all studies. The air velocity of the climatic chamber was less than 0.1 mile per hour. All subjects were clothed in pajama trousers throughout the study. Under local anesthesia, right heart catheterization was performed using a left antecubital vein. A No. 8 single lumen cardiac catheter was advanced under fluoroscopic and electrocardiographic control to the main pulmonary artery position. The left brachial artery was cannulated with a No. 18 Cournand needle. Cardiac outputs were measured by the direct Fick method during the fourth and sixth minutes in the supine resting and exercise positions at all temperature ranges. All subjects performed a standardized amount of supine exercise using a bicycle ergometer. Arterial pressures were measured over two respiratory cycles using a Statham strain gauge transducer leveled 5 cm. below the sternal angle. Heart rates were recorded electrocardiographically throughout the study. All recordings were made on the Electronics for Medicine at a paper speed of 25 mm. per second. Expired air was analyzed for oxygen and carbon dioxide by micro-Scholander analysis.[9] Arterial and mixed venous blood samples were drawn simultaneously with the gas collection and were analyzed in duplicate for oxygen content by the Van Slyke[10] and Neil methods. The only fluid which the subjects received during the time of study was that which was administered through the cardiac catheter in order to insure its patency.

Results

The individual and mean anthropometric data for all 16 subjects are shown in Table I. The mean age of this group was 27 years.

In Table II are depicted the mean values for the five subjects studied at supine rest and exercise at 78° and 100° F. A comparison of the two resting studies reveals no significant differences in oxygen consumption, cardiac output, cardiac index, or A-V oxygen differences. Similarly, no significant differences were observed in the mean values when these five subjects performed comparable levels of supine exercise at both of these temperatures. All subjects responded with an increase in heart rate when exposed to the higher ambient temperature. At rest there occurred a 15 per cent increase in heart rate and at

Table I. Individual and mean anthropometric data

	Patient	Age	Height (in.)	Weight (lb.)	BSA/M
1	J. H.	22	70	234	2.23
2.	A. C.	27	71	195	2.09
3.	W. V.	30	68	130	1.70
4	W. L.	30	70	175	1.97
5	J. K.	32	66	160	1.82
6.	J. D.	35	72	170	1.99
7	E. C.	28	73	193	2.12
8.	W. Mc.	41	70	183	2.02
9	D. R.	33	68	139	1.73
10	J. G.	23	69	140	1.78
11	A. L.	24	72	169	1.98
12.	D. D.	23	70	188	2.03
13.	E. C.	28	67	160	1.81
14	E. D.	27	71	154	1.89
15.	K. K.	22	72	188	2.07
16.	W. D.	22	78	206	2.30
Mean values		27	70.4	174	1.97

exercise a 7 per cent increase. Calculated stroke volume, therefore decreased under heat stress.

The results comparing six subjects studied at 78° and 115° F are shown in Table III Once again at nearly comparable oxygen consumptions for both the resting and exercise studies, there was no significant differences in the mean values for cardiac output and A V oxygen differences. At this level of heat stress, there occurred a 26 per cent increase in the mean values for heart rate for both rest and exercise.

Table IV compares the results obtained in five normal subjects exposed to an environmental temperature of 125 F At nearly comparable oxygen consumptions, this degree of heat stress produced an increase in mean cardiac output values for both rest and exercise. These changes in cardiac output were statistically significant ($P < 0\ 05$) A 28 per cent increase in

Table II *Results of five normal subjects tested at 78° and 100° F*

Mean Values	*Rest, Temp 78° F*	*Rest Temp 100° F*	*Exercise Temp 78° F*	*Exercise Temp 100° F*
Oxygen consumption (ml./min /M)	131 ± [illegible]	138 ± 17	381 ± 46	373 ± 37
Cardiac output (L./min.)	5 48 ± 0 7	5 60 ± 0 8	9 25 ± 1 6	8 84 ± 2 3
Cardiac index (L./min.)	2 80 ± 0 2	2 87 ± 0	4 74 ± 0 9	4 56 ± 1 2
Stroke volume (ml.)	84 ± 9	76 ± 9	89 ± 12	81 ± 23
Heart rate	65 ± 5	75 ± 9	105 ± 7	114 ± 3
A V oxygen diff (vol. %)	4 5 ± 0 3	4 6 ± 0 4	7 9 ± 0 9	7 8 ± 1 2

Table III *Results of six normal subjects tested at 78° and 115° F*

Mean Values	*Rest, Temp. 78° F*	*Rest Temp 115° F*	*Exercise Temp 78° F*	*Exercise Temp 115° F*
Oxygen consumption (ml./min /M)	125 ± 20	137 ± 13	435 ± 89	430 ± 85
Cardiac output (L./min)	6 .3 ± 1 0	6 61 ± 0 9	11 23 ± 0 6	11 36 ± 0 4
Cardiac index (L./min.)	3 49 ± 0 4	3 49 ± 0 8	5 89 ± 0 6	5 95 ± 0 5
Stroke volume (ml.)	84 ± 5	71 ± 3	98 ± 9	82 ± 13
Heart rate	76 ± 6	96 ± 3	108 ± 7	137 ± 4
A-V oxygen diff (ol. %)	3 8 ± 0 5	4 0 ± 0 2	7 3 ± 0 7	7 1 ± 0 9

Table IV *Results of five normal subjects tested at 78° and 125 F*

Mean Values	*Rest, Temp 78° F*	*Rest, Temp 125° F*	*Exercise Temp 78° F*	*Exercise Temp 125° F*
Oxygen consumption (ml./min./M)	122 ± 17	129 ± 18	477 ± 39	483 ± 41
Cardiac output (L./min.)	5 30 ± 0 3	7 07 ± 0 9	11 85 ± 0 9	13 68 ± 0 9
Cardiac index (L./min.)	73 ± 0 2	3 53 ± 0 5	5 75 ± 0 3	6 78 ± 0 4
Stroke olume (ml.)	73 ± 11	73 ± 15	106 ± 14	92 ± 9
Heart rate	77 ± 10	101 ± 15	108 ± 7	157 ± 14
A V oxygen diff (Vol. %)	4 5 ± 0 4	5 6 ± 0 2	8 3 ± 0 4	7 1 ± 0 6

heat exposure is responsible for the reported increases in cardiac output. The results of this study as well as previous work do not support this contention.[12,13] In the present investigation increases in heart rate occurred in all subjects exposed to temperatures of 100° and 115° F without an increase in cardiac output.

The changes which we observed in pulmonary and brachial artery pressures are similar to the findings reported by others.[4] The calculated pulmonary and systemic vascular resistances decreased at all levels of heat stress. The mean pulmonary artery pressure during exercise at 115° F decreased even in the face of an increasing cardiac output. Although the arterial pressure changes which were recorded in this study were not statistically significant it should be noted that our subjects all had normal blood pressures. In contrast the hypertensive subjects studied by Sancetta and associates[4] demonstrated dramatic reductions in arterial pressure upon exposure to a hot dry environment.

Summary

The effects of acute heat stress (a hot dry environment) on cardiac hemodynamics were studied in 16 normal unacclimatized male subjects. The results indicate that the cardiac output obtained at a comfortable environment (78° F) remains essentially unchanged until an ambient temperature of 115° F is exceeded. At 125° F the cardiac output both at rest and during exercise is significantly increased over that obtained at 78° F. These increases in cardiac output are associated with inverse changes in A-V oxygen differences. A decrease in the mean pulmonary and brachial artery pressures occurred over the full range of temperatures studied.

REFERENCES

1. Grollman, A.: Physiological variations of the cardiac output in man. V. Am. J. Physiol. 95:263, 1930.
2. Burch, G. E., and Hyman, A.: Influence of a hot and humid environment upon cardiac output and work in normal man and in patients with congestive heart failure at rest, Am. Heart J. 53:665, 1957.
3. Burch, G. E., and DePasquale, N. P.: Hot climates, man and his heart, Springfield, Ill., 1962, Charles C Thomas, Publisher.
4. Sancetta, S. M., Kramer, J., and Husni, E.: The effects of dry heat on the circulation of man. I. General Hemodynamics, Am. Heart J. 56:212, 1958.
5. Koroxenidis, G. T., Sheppard, J. T., and Marshall, R. T.: Cardiovascular response to acute heat stress, J. Appl. Physiol. 16:869, 1961.
6. Carlsten, A., Gustafson, A., and Werko, L.: Hemodynamic influence of warm and dry environment in man with and without rheumatic heart disease, Acta med. scandinav. 169:411, 1961.
7. William, C. E., Bredell, G. A., Syndham, C. H., Strydom, N. B., Morrison, J. F., Peters, J., Fleming, P. W., and Ward, J. S.: Circulatory and metabolic reactions to work in heat, J. Appl. Physiol. 17:625, 1962.
8. Consolazio, C. F., Matoush, L. O., Nelson, R. A., Torres, J. B., and Isaac, G. J.: Environmental temperature and energy expenditures, J. Appl. Physiol. 18:65, 1963.
9. Scholander, P. R.: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples, J. Biol. Chem. 167:235, 1947.
10. Peters, J. D., and Van Slyke, D. D.: Quantitative clinical chemistry—methods, Baltimore, 1932, The Williams & Wilkins Company, vol. 2.
11. Rowell, L. R., Blackman, J. B., Martin, R. H., Mazzorella, J. A., and Bruce, R. A.: Hepatic clearance of indocyanine green in man under thermal and exercise stresses, J. Appl. Physiol. 20:384, 1965.
12. Stein, E., Damato, A. N., Kosowsky, B. D., Lau, S. H., and Lister, J. W.: The relation of heart rate to cardiovascular dynamics. Pacing by atrial electrodes, Circulation 33:925, 1966.
13. Ross, J., Linhart, J. W., and Braunwald, E.: Effects of changing heart rate in man by electrical stimulation of the right atrium, Circulation 32:549, 1965.

Hemodynamic effects of beta-adrenergic blockade at controlled ventricular rates

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Beta-adrenergic blocking agents have both chronotropic and inotropic effects which may be competitive or additive. The present studies were designed to eliminate the chronotropic effects and thus allow analysis of inotropic effects operating alone. Dogs in which the ventricular rate could be electrically controlled over a wide range because of previously induced complete heart block, were studied at fixed ventricular rates before and after the administration of propranolol. In addition to pressure and flow measurements, rapid sequential changes in left ventricular volume were studied with biplane cineangiocardiography.

Materials and methods

Complete heart block was induced by ligation of the bundle of His in 8 mongrel dogs weighing from 15 to 22 kilograms. Following a recovery period of at least 2 weeks, each dog was anesthetized with an intravenous injection of 3 ml. per kilogram of a solution containing 1.6 grams of chloralose and 16 grams of urethane per 100 ml. Respirations were controlled with an endotracheal tube and a Harvard respirator. Ventricular rate was regulated with an external Corbin Farnsworth pacemaker connected to a No. 6 F bipolar electrode catheter which had been placed in the right ventricle via a jugular vein. Intravascular pressures were monitored with Statham P23D transducers connected to No. 8 F Lehman catheters placed in the right atrium via a femoral vein, in the right ventricle via the opposite femoral vein, and/or in the left ventricle via a femoral artery. Arterial pressure was recorded from a No. 18 Cournand needle in the opposite femoral artery. Mean pressures were obtained by electrical integration.

Cardiac output was estimated by a previously described[1] indicator dilution technique in which indocyanine green dye was injected into the right atrium while blood was being continuously sampled from the femoral artery. The indicator dilution curves were obtained with a Gibson densitometer and were recorded on a DR-8 Electronics for Medicine photographic recorder, as were the pressure tracings and the electrocardiogram (ECG).

In 5 dogs arterial, right atrial, and right

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ventricular pressures as well as duplicate indicator dilution curves were recorded at the idioventricular rate and ventricular rates of approximately 68 110 and 180 beats per minute before and 10 minutes after an intravenous injection of 0 2 mg per kilogram of propranolol The dog was allowed to stabilize for 10 minutes at ea h ventricular rate before hemodynamic measurements were made The order in which the response at arions ver tricular rates were studied was randomized before and after the drug

In 3 additional dogs, the above measurements were limited to a ventricular rate of 66 to 69 but biplane left ventricular cineangiocardiograms were obtained before and after propranolol in order to calculate changes in left entricular volume. In addition to the No 8 F Lehman catheter placed in the left ventricle to monitor pressure a No 8 F Gensini catheter was placed ii the left ventricle via the carotid artery in order to inject contrast material The dogs were positioned in a slight right anterior oblique position in order to clear the cardiac shadow from the spine

Using a Picker biplane cinefluorography system the cineangiocardiograms were taken at 60 frames per second on 35 mm fil n during the hand injection of 25 ml of sodiu iothalmate 80 per cent (Angio Conra)* into the left ventricle All cineangiocardiograms were taken with the respirator stopped at maximu n inspiration Pressure and electrocardiographic events recorded on paper were related to angiographic events by a metal rod which moved in the x ray field while a mark was simultaneously inscribed on the recording paper each time an R wa e was generated

The 35 mm negati es were reduced to 16 mm films. Individual opacified left ventricular silhouettes from the corresponding lateral and anterior posterior (A P) cineangiocardiograms were projected and drawn on paper Life-sized dimensions were obtained by altering the film projection distance so that the projected size of an aluminum model which was filmed with the image intensifier tubes in the same position as they were during the study matched the true dimensions of the model

Ventricular volumes were calculated from the A P and lateral ventricular silhouettes utilizing the formula for the volume of an ellipsoid as described by Dodge and associates.[8] In this laboratory estimates of ventricular volume calculated in the postmortem dog heart from biplane cineangiocardiograms correlated well with ventricular volume determinations measured by incremental injections of barium paste into the postmortem ventricle. In a series of 44 observations the correlation coefficient was 0 994 and the standard error of the estimate was ±2 28 ml

In addition preliminary studies demonstrated that there was a good correlation between left ventricular stroke volumes calculated from indicator dilution cardiac output estimates and those determined from cineangiocardiographic frames. Duplicate green dye indicator dilution curves† were obtained in 16 dogs. Stroke volumes were calculated from the cardiac output and the heart rate noted during the inscription of the indicator dilution curves. Biplane cineangiocardiograms were then obtained and stroke volumes calculated from end-systolic and end-diastolic chamber volumes. Comparison of stroke volumes determined from indicator dilution and cineangiocardiographic techniques demonstrated a correlation coefficient of 0 976 and a standard error of the estimate of ±1 44 ml

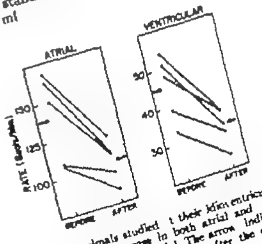

Fig 1 All animals studied t their idioventricular rates showed decrease in both atrial and ventricular rate after propranolol. The arrow indic t mean values for rate before nd after the drug

*Kindly supplied by Dr Alex Schagren-Edwards, Laboratories, New York, N Y
†Kindly supplied by Dr James Peterson, Mallinckrodt Co St. Louis, Missouri.

Individual ventricular volumes were plotted consecutively through several cardiac cycles and then connected by a line of best fit. Care was taken to choose cardiac cycles with identical P R intervals for calculation of ventricular volume before and after propranolol. End-diastolic volume was defined as the maximum volume end-systolic volume was defined as the minimum volume. Total left ventricular stroke volume was the difference between the two. Forward left ventricular stroke volume was determined by dividing the indicator dilution cardiac output per minute by the heart rate The regurgitant stroke volume was determined by subtracting the forward stroke volume from the total left ventricular stroke volume Ejection fraction was defined as that portion of the end-diastolic volume which was ejected and it was expressed as a percentage.

Utilizing the ventricular volume curves and the simultaneously measured left ventricular pressures left ventricular pressure volume loops were constructed Pressure volume work was calculated from the pressure volume loops. The area beneath the ejection portion of the loop indicated the work of the left ventricle in ejecting blood The following formula was utilized

Pressure lume work (PVW) =
PV × 1.36 × 10 × 1.055

Where

PV = area beneath the ejection portion of the pressure volume loop in cm. multiplied by the scale factor for pressure and volume

1 36 × 10 = factor for conversion of mm. Hg to Gm.M

1 055 = specific gravity of blood.

Total peripheral resistance was calculated by dividing the mean arterial pressure (mm. Hg) by the cardiac output (liter per minute) and expressed in arbitrary units. The mean systolic ejection rate was calculated by dividing the cardiac output (milliliter per minute) derived from indicator dilution curves by the duration of systole per minute (second per minute) derived from the arterial pulse tracings. The data were examined statistically with the paired T Test

Results

The negative chronotropic effect of propranolol is well illustrated in Fig 1 In 5 dogs which were studied at their idioventricular rate, the mean atrial rate

Table I Hemodynamic findings before and after propranolol at a controlled ventricular rate of 66 to 69

Dog No.	Cardiac output (L./min.)		Forward stroke volume (ml.)		R.V. end-diastolic pressure (mm Hg)		Arterial pressure (mm. Hg) Systolic		Diastolic		Mean		Total peripheral resistance (units)		Mean systolic ejection rate (ml./sec.)	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
1	3 22	1 31	49	20	5	7	265	190	90	112	122	133	38	102	132	104
2	3 44	2 63	51	40	8	9	190	155	95	90	125	107	[illegible]	41	241	153
3	2 93	2 60	38	37	7	8	190	196	100	85	138	120	47	46	187	170
4	1 69	1 32	27	20	8	8	191	1 3	71	74	104	107	62	[illegible]	146	95
5	2 21	2 45	33	32	8	9	165	180	80	85	103	112	47	48	186	129
6	2 18	1 23	32	18	9	9	183	152	98	98	120	123	55	102	176	111
7	2 64	1 67	38	24	6	9	145	140	87	[illegible]	110	120	24	73	218	127
8	3 52	[illegible] 82	51	12	3	4	200	110	120	75	155	87	44	110	233	59
Mean	2 72	1 74	40	25	7	8	191	162	93	88	122	114	44	75	196	119
S.D ±	0 65	0 69	9	10	2	2	33	29	13	12	18	14	12	23	50	33
	P < 0 05		P < 0 01		P < 0 02		P < 0 10		P = NS		P = NS		P < 0 05		P < 0 02	

C Control, P after propranolol (0.2 mg. per kilogram)

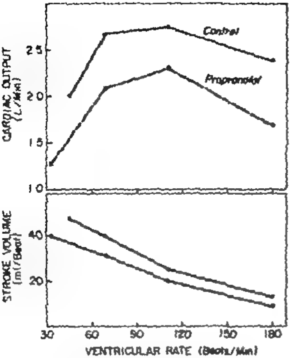

Fig 2 The mean values for cardiac output and stroke volume were consistently lower after propranolol over the entire rate range studied.

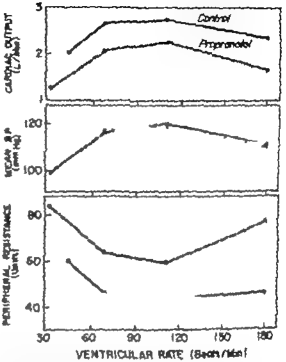

Fig. 3 Cardiac output, in the upper panel was consistently lower after propranolol Mean arterial pressure in the middle panel, was essentially the same before and after propranolol except at the idioventricular rate. This discrepancy was due to the markedly lower ventricular rate in the unpaced dogs after propranolol. The peripheral resistance, in the lower panel was consistently increased after propranolol.

fell from 139 to 103 and the ventricular rate from 45 to 32 after propranolol

Table I lists the changes associated with the administration of propranolol (0 mg per kilogram) when the ventricular rate was controlled at 66 to 69 beats per minute After propranolol there was a significant fall in mean cardiac output from 2 ? to 1 74 L per minute in stroke volume from 40 to 25 ml and in mean systolic ejection rate from 196 to 119 ml per second Mean right ventricular end diastolic pressure rose from 7 to 8 mm. Hg The arterial systolic pressure fell in 4 of 8 animals and the mean decrease in the whole group was from 191 to 162 mm. Hg but this was not significant at the 5 per cent level There was little over all change in the arterial diastolic or mean pressures. The decrease in cardiac output in the face of the unchanged mean arterial pressure accounted for the significant increase in calculated peripheral resistance from 44 to 75 units.

Fig ? demonstrates that this pattern of decreased cardiac output and stroke volume was seen in 5 dogs at rates varying from the idioventricular rate to as high

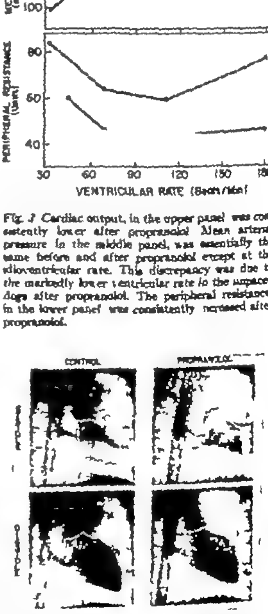

Fig 4 Selected cineangiocardiographic frames from the A-P projection in Dog 6 illustrate the increase in end-systolic size following propranolol. In this animal, incorporation of the lateral view in the calculation of end-diastolic volume indicated that this volume also increased slightly

Table II. Ventricular volume studies

Dog No.	LV volume* End-diastolic (ml.)		LV volume* End-systolic (ml.)		Total* LV stroke volume (ml.)		Ejection fraction (%)		Forward† LV stroke volume (ml.)		Regurgitant stroke volume (ml.)		Per cent regurgitation (%)	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P
6	37	41	9	19	28	22	76	54	32	18	0	4	0	22
7	73	96	22	44	51	[illegible]	70	54	38	24	15	28	34	54
8	119	116	49	70	70	46	59	40	51	12	18	24	26	5

C, Control; P, propranolol; LV, left ventricle.
*Derived from cineangiocardiograms.
†Derived from indicator dilution curves.

as 180 beats per minute. Before propranolol the mean cardiac output estimations at the idioventricular and paced rates of 68, 110, and 180 beats per minute were 2.03, 2.67, 2.74, and 2.38 L. per minute, respectively. Corresponding mean cardiac output estimations at the same rates after propranolol were 1.27, 2.08, 2.26, and 1.67 L. per minute. After propranolol stroke volume fell from 47 to 39 ml. at the idioventricular rate, from 39 to 31 at a rate of 68, from 25 to 20 at a rate of 110, and from 13 to 9 ml. at a rate of 180 beats per minute.

Fig. 3 illustrates the consistent increase in peripheral resistance seen at all ventricular rates after propranolol. It increased from 60 to 84 at the idioventricular rate, from 46 to 62 at a rate of 68, from 44 to 59 at a rate of 110, and from 46 to 77 units at a rate of 180 beats per minute. Except for values obtained at the idioventricular rate, the mean arterial pressure showed little over all change over the entire rate range before and after propranolol.

Cineangiocardiograms obtained before and after propranolol while 3 dogs were being placed at rates of 66 to 69 per minute demonstrated striking changes in left ventricular performance. Fig. 4 was obtained from the A-P cineangiocardiograms in Dog 6 during end-systole and end-diastole, before and after propranolol. The marked increase in end-systolic volume following propranolol is apparent. In this view the end-diastolic volume showed little change. However, after incorporating the lateral view into the calculation of end-diastolic volume, a slight increase in end-diastolic volume was noted. This dog developed a very small amount of mitral insufficiency after propranolol. In Dogs 7 and 8 a mild to moderate amount of mitral insufficiency was noted on the control cineangiocardiograms. This appeared to be increased after the administration of propranolol.

Table II summarizes the results of ventricular volume calculations obtained in 3 dogs. End-systolic volume increased in all 3 dogs, end-diastolic volume increased in 2 and fell slightly in one. Total left ventricular stroke volume fell in 2 animals and was unchanged in one. The ejection fraction clearly decreased in all 3 dogs. The forward stroke volume, calculated from indicator dilution curves, fell markedly in all 3 dogs despite the fact that in Dog 7 there was no change in total left ventricular stroke volume. This discrepancy is explained by the increased mitral insufficiency associated with the administration of propranolol. The increase in mitral insufficiency was easily seen on the cineangiocardiograms and was reflected by the increase in the calculated regurgitant volume from 15 to 28 ml. per beat and from 34 to 54 per cent of the total left ventricular stroke volume. It is worth noting that propranolol markedly increased the

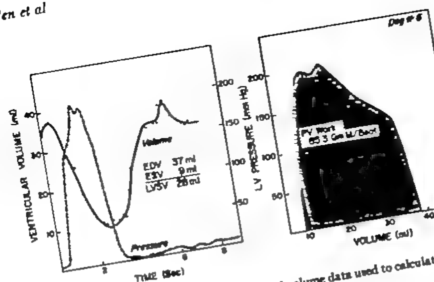

Fig. 5. The left hand panel illustrates the pressure values and volume data used to calculate the pressure volume loop in the right hand panel before administration of propranolol.

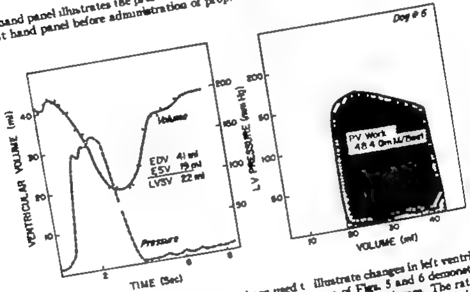

Fig. 6. The same conventions as those in Fig. 5 have been used to illustrate changes in left ventricular pressure, volume, and the pressure volume loop after propranolol. Comparison of Figs. 5 and 6 demonstrates that propranolol lead to an increase in left ventricular end-diastolic and end-systolic volumes. The rate of ventricular emptying was slower after propranolol as indicated by the more gradual downward slope of the volume curve in Fig. 6. The decreased area and therefore decreased pressure volume work after propranolol is apparent when the two loops are compared.

amount of mitral regurgitation in Dogs 7 and 8 which were observed to have mitral insufficiency during the control cineangiocardiograms and propranolol administration apparently led to the development of a small amount of mitral insufficiency in Dog 6 which had none during the control cineangiocardiogram.

The pressure volume relationships and changes associated with beta adrenergic blockade are illustrated in Figs. 5 and 6. Examination of the ventricular volume curves indicates that the dog ejected less blood from a larger end-diastolic volume at a slower rate after propranolol. The pressure volume loops demonstrate the decreased area in the loops which led to the calculation of decreased left ventricular work after propranolol.

Discussion

The alterations in pressure and flow following propranolol noted in the present study are in general accord with those observed in previous experiments involving dogs.[3] The decrease in atrial and ven

tricular rates after propranolol (Fig 1) illustrates the negative chronotropic effect of the drug which has been seen in numerous studies. Murray and co-workers[6] did not note a decrease in heart rate in a comparable series of dogs. They also failed to find a decrease in cardiac output and therefore stroke volume. The present studies as well as others,[4] have noted such a decrease. The profound decreases in cardiac output induced by propranolol in these studies may be due to the direct effects on the contractile process in cardiac muscle and partially to several other factors. Propranolol may block the positive inotropic effect of circulating catecholamines. It may be speculated that animals with chronic heart block which have not been paced prior to the experiment may be under increased sympathetic drive to maintain an adequate cardiac output. In addition increased degrees of sympathetic tone are believed to be a product of chloralose anesthesia.[7,8] The decrease in coronary blood flow noted by McKenna and his associates[4] following propranolol administration in dogs may also have contributed to the fall in cardiac output noted in the present studies. The increase in peripheral resistance in this and other studies may be a manifestation of the blockade of the vasodilator influence of beta receptors and to reflex stimulation of alpha-receptors to maintain arterial pressure in the face of falling cardiac output.

The control of cardiac rate as carried out in this study allowed the demonstration of the negative inotropic effect of propranolol without the modifying influence of the negative chronotropic effects. That these effects are not limited to any particular rate range is indicated by Figs. 2 and 3 in which it can be seen that cardiac output and therefore stroke volume fell over the entire rate range studied. In preliminary studies utilizing the heart block animal preparation it was found that the combination of negative chronotropic and inotropic effects of the drug could be so profound that the animals frequently had to be paced after the administration of propranolol in order to prevent death. Donoso and colleagues[9] reported a somewhat similar study in which propranolol was administered to patients with complete heart block and fixed-rate implanted cardiac pacemakers. They noted similar declines in cardiac output.

The biplane left ventricular volume studies shed further light on the effects of propranolol. In all 3 animals, the striking increase in end-systolic volume following propranolol was apparent from the cineangiographic film before the volume calculations were made. In 2 of the animals the end-diastolic volume remained approximately the same whereas in Dog 7 there was a striking increase in end-diastolic volume. The ejection fraction fell in all 3 animals as did the forward left ventricular stroke volume. The cineangiographic studies also add a note of caution to the interpretation of hemodynamic data which might be insensitive to varying degrees of mitral insufficiency during a study. It was of particular interest to note that the regurgitant stroke volume increased in all 3 animals after propranolol. In Dog 6 the development of the seemingly inconsequential mitral regurgitation of 4 ml. was noted during preliminary viewing of the cineangiographic film before the volume calculations confirmed the small amount of regurgitation. The increases in per cent regurgitation following the administration of the drug emphasized that classical hemodynamic observations dependent solely upon the measurement of pressure and forward flow from the left ventricle may not give a true picture of the extent of abnormalities in ventricular function following the administration of beta-blocking agents.

The increase in mitral regurgitation may be explained on several bases. Since the left ventricle which may already be compromised by the negative inotropic effects of propranolol is facing an increased peripheral resistance and an unchanged mean aortic pressure it would not be surprising that an increased percentage of its total stroke volume might be regurgitated into the lower pressure left atrium. This mechanism would be particularly appropriate in the animal which even before the administration of propranolol has a significant degree of mitral insufficiency as did Dogs 7 and 8. It is also possible that the administration of a negative inotropic

agent may alter the sequence of contraction in the left ventricle in such a way that the normal function of the papillary muscles is not operative so that the mitral leaflets do not become firmly approximated at the appropriate time in the cardiac cycle.

The only other observations concerning left ventricular volume changes following the administration of propranolol are those reported by Murray and associates. These workers utilized the thermodilution technique to document changes in left ventricular volume after the administration of 0.5 mg. per kilogram of propranolol. While the thermodilution technique does not allow the detection of unsuspected mitral regurgitation, the data is in essential agreement with the present findings. For reasons which are not clear from the protocol, these authors did not note decreases in heart rate, stroke volume, or cardiac output as were noted in the present studies. The absence of the decrease in heart rate makes the volume observations in the studies of Murray and associates comparable to the present studies in which ventricular rate was not allowed to change. Of 7 dogs studied by Murray and associates, the end-diastolic volume increased in 5, decreased in 1, and showed little change in 1. The end-systolic volume increased in 6 animals and showed little over-all change in the remaining animal. Recalculation of their data indicates that the ejection fraction fell in all 7 animals.

The observation that ventricular end-diastolic pressure increases in the face of an increasing or unchanging end-diastolic volume would be compatible with the concept that the drug has induced a decrease in ventricular distensibility. This would be in keeping with the observations of Hefner and colleagues[7] who noted that epinephrine has the opposite effect of increasing diastolic distensibility. While these explanations seem plausible, they are contradictory to those of Mitchell and co-workers[8] who found that adrenergic activity did not change the pressure fiber length characteristics of the ventricle. It is also possible that further distensibility of the ventricle was limited or altered not by the drug but rather by the restriction imposed by the surrounding pericardium.

Summary

Hemodynamic studies were performed before and after the administration of 0.2 mg. per kilogram of propranolol to dogs with surgically induced complete heart block which were maintained at controlled ventricular rates varying from the idioventricular rate to 180 beats per minute. At all ventricular rates studied administration of propranolol led to a decrease in cardiac output and therefore stroke volume as well as an increase in peripheral resistance and ventricular end-diastolic pressure. Left ventricular volume studies in 3 animals indicated that there was a variable increase in end-diastolic volume, an easily observed and calculated increase in end-systolic volume and mitral regurgitation as well as a striking decrease in ejection fraction. These studies in which the negative chronotropic effect of propranolol were eliminated emphasize the markedly negative inotropic effects of the drug. The volume studies not only emphasize the inability of the ventricle to eject blood into the aorta but they also illustrate that propranolol can produce variable changes in mitral insufficiency. Variations in or the development of mitral insufficiency may alter conclusions drawn from hemodynamic data which do not include angiographic observations.

REFERENCES

1. Taufic, M., Bashour, R. A., and Lewis, F. J.: Production of heart block in dogs under direct vision, Surg. Forum 5:96, 1955.
2. Miller, D. E., Gleason, W. L., and McIntosh, H. D.: Comparison of cardiac output determination by the direct Fick method and the dye dilution method using indocyanine green dye and a cuvette densitometer, J. Lab. & Clin. Med. 59:345, 1962.
3. Dodge, H. T., Sandler, H., Ballew, D. W., and Lord, J. D., Jr.: Use of biplane angiocardiography for the measurement of left ventricular volume in man, AM. HEART J. 60:762, 1960.
4. McKenna, D. H., Corliss, R. J., Sialer, S., Zarnstorff, W. C., Crumpton, C. W., and Rowe, G. G.: Effect of propranolol on systemic and coronary hemodynamics at rest and during simulated exercise, Circulation Res. 19:520, 1966.
5. Nakano, J., and Kusakari, T.: Effect of beta adrenergic blockade on the cardiovascular dynamics, Am. J. Physiol. 210:833, 1966.
6. Murray, J. F., Escobar, E., Jones, N. L., and Rappaport, E.: Hemodynamic effect of th-

beta-adrenergic blocking drugs in anesthetized intact dogs, Am. Heart J 72:38, 1966.

7 Bass, B. G and Buckley N M: Chloralose anesthesia in the dog: A study of drug actions and analytical methodology Am. J Physiol. 210:854, 1966.

8. Vincent, S., and Thompson, J H.: The pharmacodynamical action of chloralose, J Physiol 65:449 1928.

9 Donoso, R., Cohn, L. J Newman, B J Bloom H S Stein, W G., and Friedberg, C. K. Effects of propranolol in patients with complete heart block and implanted pacemakers, Circulation (Suppl. III) 31:99 1966.

10 Hefner L. L. Coghlan, H. C Jones, W B and Reeves, T J Distensibility of the dog left ventricle, Am. J Physiol. 201:97 1961

11 Mitchell, J H. Linden, R. J and Sarnoff S. J Influence of cardiac sympathetic and vagal nerve stimulation on the relation between left ventricular diastolic pressure and myocardial segment length, Circulation Res. 8 1100 1960.

Humoral factors in massive pulmonary embolism: An experimental study

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Pulmonary embolism in man can result in pulmonary hypertension, airway constriction, and death. These effects at times seem out of proportion to the amount of emboli found in the lung. Nevertheless, it is generally assumed that mechanical obstruction of the pulmonary vasculature is the major determinant of the manifestations of this disease. The importance of extramechanical effects resulting from the liberation of humoral substances or from neurogenic reflexes has not been established and their significance has usually been minimized.

In previous studies we have found evidence that airway constriction associated with experimental pulmonary embolism is related to the release of serotonin from platelets.[1] We have also demonstrated that a thick accretion of degranulated platelets is present on fresh thromboemboli removed from the lungs of animals, and we have observed that lethality from experimental pulmonary embolism is related significantly to the number of circulating platelets.[2] A humoral mechanism may also be involved in the airway constriction seen in patients with pulmonary embolism.[3,4] The present study demonstrates the role of extramechanical factors in increasing the resistance to blood flow through the lungs and suggests that reversible humoral effects are important following pulmonary embolism.

Since the manifestations of mechanical obstruction or severe vasoconstriction are virtually identical, their distinction experimentally and clinically has been difficult. In this study, a pharmacological separation of mechanical and humoral effects was made. Animals were embolized in a uniform manner with fresh and aged autologous venous thrombi. The effects of embolization on the central venous pressure (CVP) and on the circulating platelet count were measured. Emboli were examined microscopically for the presence of platelets on their surface. The effects, respectively, of heparin, an inhibitor of monoamine oxidase (MAO) which raises the serotonin content of platelets, and a serotonin antagonist were evaluated.

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Methods and materials

All experiments were performed on New Zealand white rabbits weighing 2 to 3 kilograms and anesthetized with intravenous Nembutal (30 mg per kilogram) The jugular veins were exposed bilaterally On one side, a 4 cm Y-shaped segment of jugular vein and its two major tributaries were isolated distended with blood and clamped off at either end One NIH unit of thrombin (Parke Davis and Co Detroit Mich.) was then introduced with a 25 gauge needle into the large, distended venous segment. Provided care was taken in withdrawing the needle after the injection of thrombin, no bleeding occurred at the puncture site. Six minutes after the injection of thrombin the stasis thrombus so formed was released to the lungs.

On the other side of the neck a length of polyethylene tubing (PE 205) was introduced into the contralateral jugular vein and positioned so that the tip was just below the clavicle. The tubing was then tied into place with ligatures and the other end attached to a three-way stopcock and then to a manometer The tubing and the manometer were flushed with sufficient frequency to insure patency and the system was kept filled with saline. Pressure readings on the manometer were taken every minute over a period of 30 minutes after release of the embolus. All pressures were recorded as positive or negative deviations from the control level in millimeters of saline.

Blood was obtained for platelet counts from an indwelling polyethylene catheter in the carotid artery Platelet counts were performed immediately before and 2½ minutes after release of the embolus All platelet counts were performed using a standard Unopette (Becton Dickinson & Company Rutherford N J) and a phase-contrast microscope. All counts were performed blind by one technician and the standard error of the method (3.5 per cent) was established by blinded" duplicate counting

Animals were itially allocated into five major groups (1) a control group of 10 rabbits given no drugs (2) a heparin series in which three groups of 10 rabbits each were given 100 units, 250 units, and 500 units of heparin respectively travenously 5 minutes before release of the thromboembolus (3) a MAO inhibitor group of 10 rabbits which were given iproniazid (Marsilid F Hoffmann-La Roche & Co. Ltd Basle, Switzerland) 30 mg per kilogram intravenously daily for three consecutive days before embolization (4) a MAO inhibitor-methysergide group in which 10 rabbits were pretreated with iproniazid as described above and then given 3 mg per kilogram of methysergide (Sansert Sandoz Pharmaceuticals, Hanover N J) by means of an infusion pump (Harvard Apparatus Co Dover Mass.) the infusion of methysergide was started 20 seconds before embolization and continued for a total of 70 seconds (5) an iproniazid heparin group in which 10 rabbits were pretreated with iproniazid and then given 500 units of heparin before embolization.

At the end of each experiment, the animal was painlessly put to death and an autopsy performed After localization the embolus was carefully removed fixed in formalin and cross-sectioned for light microscopy

To evaluate the effects of an aged thrombus, an additional 20 rabbits were randomly allocated into two groups. All of the 20 animals were anesthetized as described and thrombi released at the end of one hour of anesthesia. In both groups, 0 2 mg of epsilon-aminocaproic acid (Amicar Lederle Laboratories Pearl River N Y) was infused into each segment along with the thrombin to prevent thrombolysis. In one group thrombi were formed at the end of the hour of anesthesia within 10 minutes of their release. In the other thrombi were formed immediately and aged for one hour before their release. Pressures were taken as described and platelet counts were taken just prior to release and 2½ minutes after release Autopsies were performed at the end of each experiment, 30 minutes after embolization The emboli were removed from the lungs and weighed

In order to determine the relative doses of heparin required to inhibit fibrin formation versus platelet aggregation in response to thrombin the following in vitro experiment was performed a preparation of human platelet rich citrated plasma containing approximately 250,000 platelets per cubic millimeters was prepared by centri

fugation of citrated whole blood at 220 g for 10 minutes and diluting it with an appropriate quantity of platelet poor plasma. The mixture was stirred constantly and 0.5 units of thrombin plus graded increments of heparin were added. The time of onset of platelet aggregation and fibrin formation were determined by a direct visual technique previously described.[7]

Results

The mean of all the pressure readings obtained over the 30 minute period of each experiment as well as the peak pressure level reached in each animal are graphically represented in Figs. 1 to 3. In most rabbits, peak pressures were reached within 3 minutes of embolization and then gradually declined toward the control level. An increased respiratory rate occurred in virtually all rabbits, which by itself tended to cause a fall in central venous pressure due to the increased negative intrathoracic pressure.

In the control group, the averages of the peak pressures and the mean pressures were

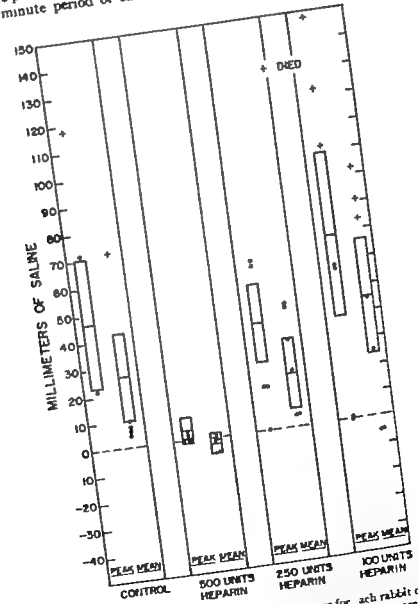

Fig. 1. Plot representing the peak and mean central venous pressures for each rabbit over 30 minutes following embolization. The average for each group of 10 rabbits and 2 standard errors are shown. The difference between the rabbits given 500 units of heparin and the control is highly significant ($p < 0.01$).

+47 and +25 mm. of saline respectively with one death occurring in this series In contrast, the rabbits given 500 units of heparin showed virtually no change in pressure after embolization with an average peak pressure being +4 mm. and an average mean pressure −2mm of saline. This difference between control and the 500 unit heparin groups is significant ($p < 0.01$) A smaller dose of heparin 250 units although sufficient to cause a six to eightfold prolongation of the glass whole blood clotting time was much less effective It resulted in an average peak pressure of +40 mm. and an average mean of +20 mm of saline which were not significantly different from the control When 100 units of heparin was given causing a two- to fourfold prolongation of the clotting time pressures higher than in the control group were observed the average peak being +69 mm and the average mean pressure +45 mm of

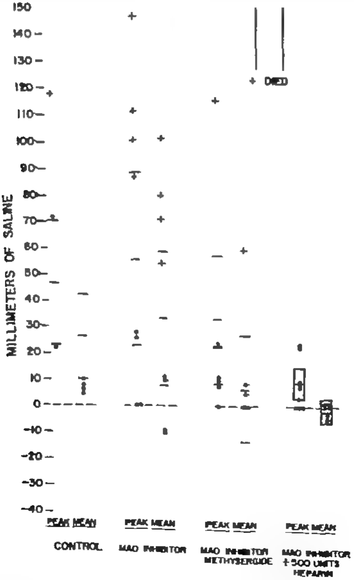

Fig 2. Representation same Fig 1 showing augmentation of pressure response and death by MAO inhibitor and nullification of this effect by methysergide. Heparin prevented the postembolic rise in CVP in animals given MAO inhibitor ($p < 0.02$).

saline there were three deaths in the group (Fig 1)

In the rabbits pretreated with iproniazid higher pressures and mortality rates compared to the control group were found following embolization The average peak pressure was +56 mm and the average mean pressure was +34 mm. of saline (Fig 2) There were four deaths in this group When both iproniazid and then methysergide were given the methysergide appeared to inhibit the previously enhanced and often lethal effect of the MAO inhibitor in all but 2 of the 10 rabbits ($p < 0.02$) The timing of the infusion of methysergide was found to be a critical factor as previously described[1] The average peak pressures of all 10 rabbits was +34 mm. and the average mean was +7 mm of saline. Similarly but more dramatically 500 units of heparin largely prevented the pressure rise in the iproniazid treated animals ($p < 0.02$) (Fig 2)

The results of the aged versus fresh emboli experiments indicated that fresh emboli induce a significantly higher CVP than do their aged counterparts (Fig 3) In the fresh emboli series, the peak and mean pressure averages were 46 and 22 mm of saline respectively whereas in the aged group the peak was 4 mm and the average mean pressure −1 mm. of saline ($p < 0.01$) The mean weight of the emboli recovered at autopsy was remarkably similar in the two groups, with considerable overlap The mean weight of the fresh emboli was 230 mg (range 152 to 366 mg) and the mean weight of the aged emboli was 221 mg (range 142 to 300 mg)

The gross findings at autopsy failed to

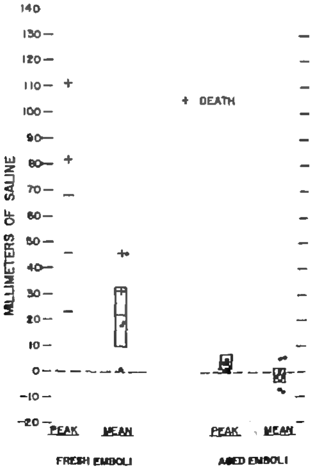

Fig 3 Central venous pressure responses in two randomly allocated groups of rabbits embolized with fresh and 1 hour-aged emboli of equivalent size ($p < 0.01$).

demonstrate any distinguishing features between any of the groups in terms of the size or location of emboli. The thromboembolus tended to be located either in the outflow tract of the right ventricle extending into the main pulmonary artery or found to be occluding the right and left pulmonary arteries having broken up en route. A photograph of a representative autopsy of an animal in which no rise in pressure occurred is shown in Fig. 4. All animals seemed massively obstructed and it was not possible from the autopsy to determine whether or not an animal had been distressed by the embolus. Microscopic sections however showed a striking distinction between some of the groups. A rim of platelets of varying thickness was seen on all the emboli with the exception of those removed from rabbits given 500 units of heparin and those aged for one hour. These latter groups showed emboli with little or no platelet material on their surface. This difference is shown on a photograph of two representative microscopic sections in Fig. 5. Electron microscopic confirmation that the rim depicted is indeed made up of platelets, has been previously published.

Similarly a substantial postembolic fall in platelet count was observed in almost all the rabbits with the exception of those given 500 units of heparin and in those in whom aged emboli were released. These findings are depicted in Fig. 6 the differences being statistically significant ($p < 0.01$).

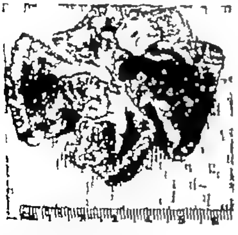

Fig. 4. Representative autopsy showing large vessel embolic occlusion of both lungs with few fragments in smaller vessels. Specimen from rabbit given MAO inhibitor and methysergide. No rise in central venous pressure occurred in this animal.

The results of the in vitro thrombin platelet heparin experiments are shown in Fig. 7. It was found that the aggregation of human platelets by thrombin can be effectively inhibited by heparin but that the dose requirement for this is considerably in excess of that necessary to block the interaction of thrombin with fibrinogen.

Discussion

Recognition of the clinical importance of pulmonary embolic disease has resulted in extensive efforts to understand its causes and manifestations. Although the effects of mechanical pulmonary vascular obstruction have been established and emphasized by numerous studies, the same cannot be said for extramechanical vasomotor responses. Due perhaps to the wide variety of experimental methods employed often involving synthetic emboli there is no agreement on the role of reflex or humoral factors, which has generally been considered to be negligible. Nelson and Smith[8] have drawn attention to the observation that embolization with synthetic materials fails to reproduce the hemodynamic effects produced by a thrombotic embolus. Pulmonary embolism is fundamentally a thrombotic disorder and certain aspects of blood coagulation may therefore need to be considered in its experimental reproduction. Consequently in the present study thrombotic emboli were used their age considered and anticoagulant drugs were controlled so as not to obscure any possible effects of the embolus. A technique of massive embolization was used since it has been claimed that large emboli in particular are unaccompanied by reflex cardiovascular disturbances.[11]

Although the CVP is a nonspecific measurement it enabled us to detect differences in response without placing a catheter within the cardiopulmonary vasculature. None of the drugs used have any known significant effect on right heart function and by themselves had no effect on CVP. Therefore, assuming no central venous spasm occurred a rise in CVP following embolization reflected a rise in right ventricular end-diastolic pressure and in the

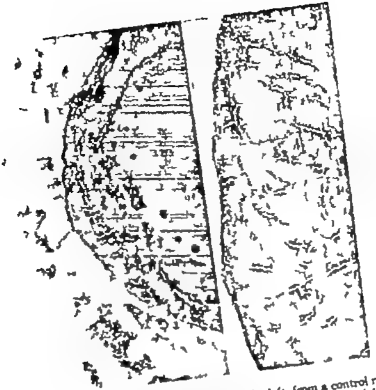

Fig. 5. Cross-sections of emboli removed from lungs (X 0). On the left, from a control rabbit showing a thick, wh tish rim composed mainly of plat lets with few scattered white cells. On the right, from a rabbit given 500 u t of heparin showing border devoid of platelet coating.

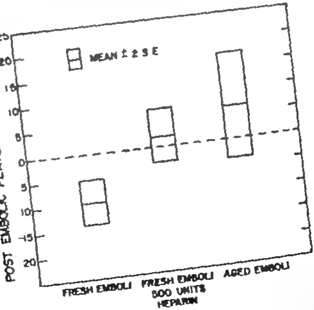

Fig. 6. Changes in platelet count 2½ min tes following embolization expressed as per cent change from the pre-embolic level. I hown the ual post-embolic f ll in platelet is significa tly inhibited by hepari or by agin the thrombus before release ($p < 0.01$).

context of these experiments indicated an increased resistance to blood flow through the lungs. No consistent gross differences were found at post mortem and any minor differences in size or location of emboli were presumably randomly distributed among the various groups. When the emboli were weighed as in the aged versus fresh thrombus series, no significant differences were detected. The observed consistent differences in CVP between certain of the groups of rabbits may therefore reasonably be attributed to nonmechanical pulmonary vasomotor effects.

The ability of heparin to prevent the usual rise in CVP following embolization was observed only with a dose of this drug sufficient to prevent platelet accretion on thromboemboli as indicated by microscopic section and platelet counts. This apparent dose specificity makes it unlikely that this effect was due to vasodilatation. The smallest dose of heparin used was, in fact, associated with a heightened CVP response, an observation which may be related to the increased platelet aggregation which has been attributed to small doses of heparin.[22] This observed therapeutic effect of heparin is presumably related to its antithrombin action which at sufficient dosage prevents the interaction of thrombin and platelets. The dose of heparin required for this is well in excess of that necessary to prevent fibrin formation through the interaction of thrombin and fibrinogen. This may be concluded from the in vivo observation in this study that the inhibition of platelet accretion on the thromboembolus required a dose of heparin about ten times greater than has been shown necessary to prevent the formation of a stasis thrombus.[1] In addition the relative dose requirements for these two effects of heparin were further demonstrated in vitro in human platelet-rich plasma to which thrombin was added (Fig. 7).

Thrombin neutralization also occurs spontaneously in vivo through the action of naturally occurring antithrombins.[23] The fact, therefore that aged thromboemboli cause significantly smaller changes in CVP than did fresh emboli of similar size provides additional support for the importance of thrombin as the trigger for the platelet-related humoral events.

The effects of iproniazid and methysergide were more modest but were compatible with the concept that the release of platelet contents contributes to the increase in pulmonary vascular resistance following pulmonary embolism and suggested that serotonin was one of the agents involved

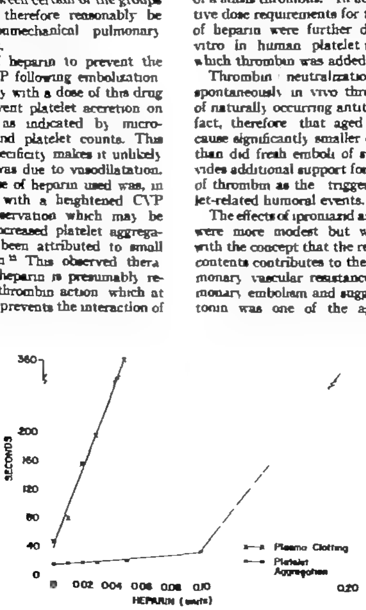

Fig. 7. In vitro study using 1 ml. of human platelet-rich plasma to which 0.5 unit of thrombin and graded amounts of heparin were added. The times required for fibrin formation and platelet-aggregation to occur are plotted. As shown, both are effectively prevented by heparin but to prevent platelet aggregation much higher dosage is required.

Iproniazid a potent inhibitor of MAO has been shown to increase the serotonin content of platelets by as much as 150 per cent [16] It is of interest therefore that MAO inhibition potentiated the effect of embolism being associated with a greater rise in CVI and a greater mortality rate This effect was nullified by the serotonin antagonist methysergide (Fig 2) Since rabbit platelets also contain histamine it is not surprising that the inhibitory effect of methysergide was less than that of heparin which presumably prevented the release of all biogenic amines. No direct measurements of free serotonin levels in the circulating blood were attempted since experimental studies have shown that serotonin essentially disappears after one circulation through the lungs.

Platelets have been described as packets of active pharmacological substances[17] among which serotonin has attracted the most interest Comroe and associates[18] suggested 15 years ago that some of the cardiorespiratory effects of pulmonary embolism were due to the liberation of serotonin from platelets in the process of blood coagulation In previous experimental studies we have demonstrated that airway constriction following thromboembolism is caused largely by the liberation of serotonin from platelets It has also been shown in animals that serotonin is one of the most potent pulmonary vasoconstrictors[1] and that virtually the entire lesser circulation is responsive to it including the large pulmonary arteries and venules.[20] Despite numerous studies however the role of serotonin or other biogenic amines carried by platelets in determining some of the cardiopulmonary responses to thromboemboli has not been established Although it has been known for some time that the infusion of serotonin and blood clot embolization produce strikingly similar effects [21] their relationship remains controversial

Daily and Moulder [22] in experiments where the dose and time of administration of the drug differed substantially from the present experiments found that after sustained pulmonary hypertension had been produced in dogs by fresh blood clot emboli it could not be reduced by the subsequent administration of methysergide. Hyman and colleagues[23] using fresh blood clot emboli found evidence for pulmonary vasoconstriction but concluded that serotonin was not involved The conclusion was based on the lack of effect produced by pretreatment with methysergide However we have found that this drug must be infused simultaneously with embolization if an effect is to be demonstrated [1] Halmagyi and co-workers [24] in cross circulation experiments in sheep demonstrated the presence of a humoral agent causing constriction of lung vessels and airways which appeared following rapid embolization with blood clot or barium sulfate. No attempt was made to identify the humoral substance. Marshall[25] was unable to detect any differences in cardiopulmonary responses when serotonin-depleted blood clot emboli were compared with those not so depleted This study however did not include consideration of the circulating platelets as being the source of serotonin Cobb and Nanson[26] confirmed the similarity in response between the effects of serotonin and blood clot emboli and showed these effects could be ameliorated by a large dose of heparin A technique of lobar embolization with autologous clots was used by Daily and associates[27] to determine whether generalized pulmonary vasoconstriction occurred and none was found However the 3 000 units per kilogram of heparin which was used to prevent coagulation would according to our data, have been more than enough to prevent vasoconstriction through the release of serotonin or other amines from platelets. Just Viera and Yeager[28] studied the effects of massive pulmonary embolism in dogs and concluded that lethality was the result of mechanical block alone and that reflex death does not occur experimentally However in these experiments aged blood clot emboli were used which we have likewise found are unattended by extramechanical events. Similarly Marshall and colleagues embolizing autologous venous thrombi [illegible] to 14 days old failed to find evidence of reflex action including little change in airway resistance or compliance in dogs whereas using fresh autologous venous thrombi we have demonstrated in dogs that striking changes in airway resistance and lung compliance occur [1]

We have been impressed by how well

mechanical obstruction of the pulmonary vasculature is tolerated by the experimental animal when unaccompanied by spasm (Fig 4) The elastic nature of the vasculature seems capable of accommodating even massive obstruction. The same degree of apparent total occlusion of the main pulmonary artery at autopsy was found in animals which displayed no untoward effects and in animals which died or developed high levels of CVP The observed differences in host response appeared rather to be related to superimposed extramechanical factors. The pharmacological content of platelets varies considerably among species and serotonin is found in much greater quantity in the rabbit than in man [26] Human parallels must, therefore, be drawn with special caution Nevertheless because of the important therapeutic implications, it is worth considering that significant, preventable cardiopulmonary responses to pulmonary embolism may be determined by the number and content of the host s circulating platelets. Of possible relevance is the old clinical observation that postoperative and postpartum states are associated with both an increase in number and stickiness of platelets, as well as an increased incidence of recognized pulmonary embolism [28]

The ability of heparin at sufficient doses to block thrombin-platelet interaction as demonstrated both in vivo (Fig 5) and in vitro (Fig 7) may be an especially useful and lifesaving property of this drug It has already been reported that bronchoconstriction associated with pulmonary embolism and thought to be platelet mediated is relieved by heparin.[4-] Vasoconstriction recently demonstrated in pulmonary embolism in man [23] may be similarly ameliorated These considerations are relevant to the successful nonoperative management of thromboembolism While the importance of massive mechanical obstruction is self evident, the present study suggests that prompt and sufficient heparin treatment may at times obviate th need for embolectomy A dose of heparin comparable on a weight basis to that found critical in this study has in fact already been reported to be superior clinically to smaller traditional doses in the treatment of acute pulmonary embolism [22,24]

Summary

Alterations in central venous pressure (CVP) were measured in response to embolization with standardized autologous venous thrombi Platelets were counted before and after embolization and their accretion on the embolus was determined microscopically at autopsy

The rise in CVP could be blocked by heparin but only at sufficient doses to prevent the platelet accretion or by aging the thrombus prior to embolization Conversely the postembolic rise in CVP and mortality rates were augmented by an inhibitor of monoamine oxidase whose effect in turn was nullified by a serotonin antagonist

It is concluded that the release of biogenic amines from platelets triggered by thrombin on the embolus, plays a significant role in the animal s response to thromboemboli.

Both in vivo and in vitro evidence is presented demonstrating that the dose requirements of heparin necessary to inhibit these events is greater than that generally used in treating pulmonary embolism.

Certain clinical observations relating to these experimental findings are reviewed and the therapeutic implications discussed

We are indebted to Dr Hugo Muench for statistical advice.

REFERENCES

1 Thomas, D P Stein, M. Tanabe G Rege, V and Wessler S. Mechanism of bronchoconstriction produced by thromboemboli in dogs, Am J Physiol 206:1207 1964
2. Thomas, D P Gurewich, V and Ashford, T P Platelet adherence to thromboemboli in relation to the pathogenesis and treatment of pulmonary embolism, New England J Med. 274:953, 1966.
3. Thomas, D P and Gurewich, V Role of platelets in sudden death induced by experimental pulmonary emboli, Circulation (Suppl. II) 32:207 1965
4 Gurewich, V Thomas, D P Stein, M., and Wessler S. Bronchoconstriction in the presence of pulmonary embolism, Circulation 27:339 1963.
5 Gurewich, V Sasahara, A and Stein, M Pulmonary embolism, bronchoconstriction and response t heparin in pulmonary embolic disease, Sasahara, A A., and Stein, M., editors New York, 1965 Grune & Stratton Inc., 312 pp.
6. Webster J R., Saadeh, G. B Eggum, P R., and Suker J R. Wheezing due to pulmonary

embolism Treatment with heparin. New England J. Med. 274:931, 1966.

7. Niewiarowski, S., and Thomas, D. P.: Platelet aggregation by ADP and thrombin, Nature 212:1544, 1966.

8. Nelson, R. J., and Smith, J. R.: The pathological physiology of pulmonary embolism. A physiologic discussion of the vascular reactions following pulmonary arterial obstruction by emboli of varying size, Am. Heart J. 58:916, 1957.

9. Marshall, R., Sabiston, D. C., Allison, P. R., Bosman, A. R., and Dunnill, M. S.: Immediate and late effects of pulmonary embolism by large thrombi in dogs, Thorax 18:1, 1963.

10. Jaques, W. E., and Hyman, A. L.: Experimental pulmonary embolism in dogs, Arch. Path. 64:483, 1957.

11. Dexter, L., and Smith, G. T.: Quantitative studies of pulmonary embolism, Am. J. M. Sc. 247:641, 1964.

12. Poole, J. C. F.: The effect of anticoagulants on artificial thrombus production, Proc. 7th Congr. Europ. Soc. Haemat. part II, 646, 1960.

13. Hensen, A., and Loeliger, E. A.: Antithrombin III. Its metabolism and its function in blood coagulation, Thromb. Diath. Haemorrh. 9 Suppl. 1, 1963.

14. Gurewich, V., and Thomas, D. P.: Pathogenesis of venous thrombosis in relation to its prevention by dextran and heparin, J. Lab. & Clin. Med. 66:604, 1965.

15. Pletscher, A., and Grey, A. F.: On the mechanism of action of monoamine oxidase inhibitors in angina pectoris, J. Am. Geriat. Soc. 9:410, 1961.

16. Thomas, D. P., and Vane, J. R.: 5-hydroxytryptamine in the circulation of the dog, Nature 216:335, 1967.

17. Rand, M., and Reid, G.: On the presence in rabbit serum of thrombotonin (thrombocytin or serotonin), Aust. J. Exper. Biol. & M. Sc. 30:153, 1952.

18. Comroe, J. H., Jr., Van Lingen, B., Stroud, R. C., and Roncoroni, A.: Reflex and direct cardiopulmonary effects of 5-OH-tryptamine (serotonin), Am. J. Physiol. 173:379, 1953.

19. Rose, J. C., and Lazaro, E. J.: Pulmonary vascular responses to serotonin and effect of certain serotonin antagonists, Circulation 6:283, 1958.

20. Sackner, M. A., Will, D. H., and DuBois, A. B.: The site of pulmonary vasomotor activity during hypoxia or serotonin administration, J. Clin. Invest. 45:112, 1966.

21. Smith, G., and Smith, A. N.: The role of serotonin in experimental pulmonary embolism, Surg. Gynec. & Obst. 101:691, 1955.

22. Daily, P. O., and Moulder, P. V.: Serotonin in pulmonary embolism, Arch. Surg. 93:348, 1966.

23. Hyman, A. L., Myers, W. D., and Myer, A.: The effect of acute pulmonary embolus upon cardiopulmonary hemodynamics, Am. Heart J. 67:313, 1964.

24. Halmagyi, D. F. J., Starzecki, B., and Horner, G. J.: Humoral transmission of cardiorespiratory changes in experimental lung embolism, Circulation Res. 14:546, 1964.

25. Marshall, R.: Serotonin and embolization by small blood clots in dogs, Thorax 21:266, 1966.

26. Cobb, B., and Nanson, F. M.: Further studies with serotonin and experimental pulmonary embolism, Ann. Surg. 151:501, 1960.

27. Daily, P. O., Griffin, A., Blackstone, E., and Moulder, P. V.: The hemodynamic effect of localized pulmonary embolism, Surg. Gynec. & Obst. 121:765, 1966.

28. Just-Viera, J. O., and Yeager, G. H.: Massive pulmonary embolism. II. Predictable mortality and cardiopulmonary changes in dogs breathing room air, Ann. Surg. 159:636, 1964.

29. Marshall, R., Sabiston, D. C., Allison, P. R., Bosman, A. R., and Dunnill, M. S.: Immediate and late effect of pulmonary embolism by large thrombi in dogs, Thorax 18:1, 1963.

30. Humphrey, J. H., and Jaques, R.: The histamine and serotonin content of the platelets and polymorphonuclear leukocytes of various species, J. Physiol. 124:305, 1954.

31. Wright, H. P.: Changes in the adhesiveness of blood platelets following parturition and surgical operations, J. Path. & Bact. 54:461, 1942.

32. Mounts, R. J., Molnar, W., Marable, S. A., and Wooley, C. F.: Angiography in recent pulmonary embolism with follow-up studies: preliminary report, Radiology 87:713, 1966.

33. Bauer, G.: Clinical experience of a surgeon in the use of heparin, Am. J. Cardiol. 14:29, 1964.

34. Kernohan, R. J., and Todd, C.: Heparin therapy in thromboembolic disease, Lancet 1:621, 1966.

The effect of spironolactone on digital vascular reactivity in essential hypertension

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It has been demonstrated that chlorothiazide decreases digital vascular reactivity to infused l-norepinephrine (NE) in patients with essential hypertension. The effect of spironolactone in this respect has not been studied. This drug is known to deplete sodium from the body with a tendency to retain potassium and, despite some disagreement, to be effectively antihypertensive. It is still not established whether all the antihypertensive effect of spironolactone is attributable to renal sodium loss or whether there is an additional direct effect on the systemic tissues. Sodium loss, moreover, can decrease blood pressure by decreasing blood volume and cardiac output in addition to its possible effect on vascular reactivity.

Fukuchi and associates found an increase in systemic pressor reactivity during spironolactone therapy, which they attributed to retention of potassium. They studied only brachial pressure responses, however, and did not inhibit sympathetic nerve discharge. Although angiotensin pressor reactivity was increased significantly by spironolactone in their study, the increase in NE pressor reactivity was not statistically significant. Because pressor reactivity went down during chlorothiazide and up during spironolactone administration, these workers attributed this effect to change in tissue potassium and found that administration of potassium chloride also increased pressor reactivity. They attributed the antihypertensive effect of both drugs, however, to sodium depletion. It was decided, hence, to determine the effect of spironolactone on vascular reactivity in patients with essential hypertension in the digit under standardized conditions, measuring pressure and flow after inhibiting sympathetic nerve discharge.

Methods

Only patients with essential hypertension were studied, those with accelerated essential, renal, or other types of hypertension having been excluded. Each subject was tested twice under the same conditions, prior to and after administration of the drug. Each test of vascular reactivity was carried out with the patient in the supine position and under 3 sets of

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Table I Effect of spironolactone on the digital circulation in 16 patients with essential hypertension

	Phase	Before spironolactone		After spironolactone		$S.E._d$†	p‡
		Mean	±S.D.*	Mean	±S.D.*		
Brachial blood pressure Systolic (mm. Hg)	A	124	37	111	22	11	< 0.3
	B	189	19	167	25	7.9	$< 10^{-4}$
	C	207	40	174	30	12	$< 10^{-4}$
Brachial blood pressure Diastolic (mm. Hg)	A	80	30	77	16	8.5	> 0.5
	B	112	11	102	15	4.7	< 0.05
	C	128	17	109	15	5.6	$< 10^{-4}$
Digital blood pressure Systolic (mm. Hg)	A	107	34	95	24	11	< 0.3
	B	167	21	150	27	8.8	$< 10^{-}$
	C	188	38	155	29	12	$< 10^{-4}$
Digital blood pressure Diastolic (mm. Hg)	A	73	21	67	15	6.3	< 0.4
	B	100	9	91	13	4.1	< 0.05
	C	115	10	97	18	6.5	$< 10^{-4}$
Effective mean digital blood pressure (mm. Hg)	A	73	24	65	19	7.6	< 0.3
	B	115	15	103	15	5.6	< 0.05
	C	128	24	106	19	7.6	$< 10^{-4}$
Digital blood flow (cm.³/cm.² skin/min.)	A	0.27	0.049	0.26	0.067	0.021	> 0.5
	B	0.14	0.062	0.18	0.070	0.024	$< 10^{-4}$
	C	0.26	0.049	0.28	0.073	0.023	< 0.5
Radius equivalent (10^{-4} cm.)	A	2.9	0.24	2.9	0.14	0.071	> 0.5
	B	2.4	0.17	2.5	0.20	0.063	< 0.2
	C	2.6	0.31	2.8	0.16	0.076	< 0.05
Work of vasoconstriction (10^{8} ergs)	B	2.8	1.1	2.0	1.4	0.47	$< 10^{-4}$
	C	1.5	0.79	0.90	0.45	0.23	$< 10^{-4}$
Rate of NE base infusion (μg/min.)	C	4.3	1.1	4.3	0.77	0.33	> 0.5
Work of vasoconstriction (ergs/μg NE base/min.)	C	*350*	*131*	*209*	*97*	*41.0*	$< 10^{-4}$

A, After vasodilatation; B, before vasodilatation; and C, after vasodilatation and infusion of l-norepinephrine (NE).
*S.D., Standard deviation.
†S.E.$_d$, Standard error of the difference.
‡p, Probability that the difference is due to chance.

conditions. (1) Phase B supine and at rest under standardized conditions (room temperature 26 to 29° C.). (2) Phase A after vasodilatation produced by indirect heating of the patient with a cradle baker over the trunk until positive heat balance was attained as manifested by copious diaphoresis. At this point 0.8 mg. per kilogram of trimethaphan camphorsulfonate (TMCS) was administered intravenously. This method inhibits approximately 90 per cent of sympathetic nerve mediated vasoconstriction in the fifth finger when compared with ulnar nerve procaine blockade.[12] (3) Phase C after vasodilatation plus NE, consisted of keeping conditions in Phase A constant together with infusion of NE and additional TMCS. The rate of infusion was so regulated by an infusion pump as to raise the brachial blood pressure to about the same level as, or 20 mm. Hg above, the starting pressure (pressure in Phase B). The infusion fluid was 5 per cent dextrose in water and contained 12 μg per cubic centimeter of l-NE and 1 mg. per cubic centimeter of TMCS. Tests for chemical interaction between TMCS and NE were negative.

In each phase digital blood flow was measured calorimetrically and systolic

*Since all work calculations are based on the degree of vasoconstriction from the dilated state, this basic phase is called Phase A. Temporally, however, the circulation in the resting state is measured first, the dilated state, second, and during norepinephrine infusion, third, as indicated numerically in the text.

and diastolic digital pressures were measured by a Gaertner capsule. Mean pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. From the mean digital blood pressure thus obtained a calculated venous pressure was subtracted.[3] The radius equivalent of the digital circulation was computed from the digital blood flow and effective mean digital blood pressure by using Poiseuille's law. The length factor for the digital circulation was calculated and considered to be constant and was corrected for variations in fingertip size.[3] In the constricted states, Phases B and C, corrections were made for critical closing pressure and/or apparent change in blood viscosity. The work of vasoconstriction for the digital circulation was estimated from the following formula:

$$w = 197 P_1 (r_1^4 - r_2^4) - \frac{16.1 P_1 (r_3^4 - r_2^4)}{Q}$$

in which w is work in ergs, P_1 is effective mean pressure and Q is blood flow in the dilated state (Phase A), r_1 is radius equivalent during vasodilatation (Phase A), r_2 is radius equivalent in the resting state (Phase B), and r_3 is the radius equivalent during vasoconstriction replacing r_2 when work of vasoconstriction produced by NE is measured. From the work thus estimated and the rate of infusion of NE, the work per microgram of NE base per minute is calculated.[3,4]

Results

It can be seen from Table I that both brachial and digital supine blood pressure as well as the work of vasoconstriction produced by NE were decreased significantly after treatment with spironolactone. There were only minimal changes in blood flow and other calculated data (Table I).

Discussion

Sodium depletion by spironolactone as well as by chlorothiazide or its congeners[1] decreases erect and supine blood pressure as well as digital vascular reactivity in essential hypertension. It seems probable that the decrease in reactivity caused the decrease in blood pressure although this is not proved by these data. Since spironolactone retains potassium in the body in contrast to chlorothiazide which depletes the body of potassium, the antihypertensive effect of both drugs cannot be attributed to potassium loss. For the same reason neither can the decrease in vascular reactivity be attributed to potassium loss but rather to sodium depletion as such. The results obtained by Fukuchi and associates[11] could have been due to baroreceptor effects or cardiac output changes rather than to intrinsic reactions of the peripheral blood vessels, unless the systemic vasculature as a whole and the digital blood vessels respond discordantly.

Summary

1. Spironolactone was administered (100 mg daily) to 16 hypertensive patients for 2 weeks.

2. Brachial and digital blood pressures and digital blood flow (calorimetric) were measured before and after vasodilatation by indirect heat supplemented by ganglion blockade as well as during the intravenous administration of l-norepinephrine (NE). These measurements were made before and at the end of the drug period and from the data changes in digital vascular caliber and work of vasoconstriction were calculated.

3. The drug produced a statistically significant decrease in supine brachial and digital blood pressure and in digital vascular reactivity to NE.

4. These decreases seem attributable to sodium depletion by the drug.

We are indebted to Dr. Stephen N. Preston of Hoffman-La Roche, Inc., for supplies of trimethaphan camphorsulfonate (Arfonad) and to Dr. William McGovern of G. D. Searle and Co. for supplies of spironolactone (Aldactone), also the secretarial assistance of Miss Arlene Fruchter and Mrs. Ina N. Solomon is appreciated.

REFERENCES

1. Mendlowitz, M., Naftchi, N., Weinreb, H. L., Gitlow, S. E., and Wolf, R. L.: The effect of chlorothiazide and its congeners on the digital circulation in normotensive subjects and in patients with essential hypertension, Ann. New York Acad. Sc. 88:964, 1960.
2. Bartter, F. C.: The mode of action of spironolactone and their use in the diagnosis of aldosteronism. In Bartter, F. C., editor: The clinical use of aldosterone antagonists, Springfield, Ill., 1960, Charles C Thomas, Publisher, page 2.
3. Hollander, W. H., Chobanian, A. V., and Wilk

ins, R. W. The antihypertensive actions of mercurial thiazide and spironolactone diuretics, *in* Buchborn, F. and Bock, K. D., editors: Diuresis and diuretics, International Symposium, Berlin, 1959, Springer Verlag, p. 297.
4. Grenfel, R. F., Briggs, A. H., and Holland, W. C.: A double-blind evaluation of antihypertensive drugs, Angiology 15:163, 1964.
5. Georgopoulos, A. J., Dustan, H., and Page, I. H.: Spironolactone in hypertensive patients, Arch. Int. Med. 108:389, 1961.
6. Hollander, W. H.: Aldosterone antagonists in arterial hypertension, Heart Bull. 12:108, 1963.
7. Grieble, H. G., and Johnston, L. C.: Treatment of arterial hypertensive disease with diuretics. I. Effects on blood pressure of bendroflumethiazide, potassium chloride and spironolactone, Arch. Int. Med. 110:26, 1962.
8. Winer, B. M.: Effects of an aldosterone antagonist and a benzothiadiazine individually and in combination in benign hypertension, Circulation 24:1073, 1961 (abstr.).
9. Wolf, R. L., Mendlowitz, M., Roboz, J., Styan, G. P. H., Kornfeld, P., and Weigl, A.: Treatment of hypertension with spironolactone, J.A.M.A. 198:1143, 1966.
10. Johnston, L. C., and Grieble, H. G.: Treatment of arterial hypertensive disease with diuretics. V. Spironolactone, an aldosterone antagonist, Arch. Int. Med. 119:225, 1967.
11. Freis, E. D.: The effects of salt and extracellular fluid depletion on vascular responsiveness with particular reference to chlorothiazide. Proc. Council for High Blood Pressure Res., Am. Heart Ass. 7:6, 1958.
12. Ikuchi, S., Hanata, M., Thakahashi, H., Lemura, H., and Goto, K.: Relationship between vascular reactivity and intracellular potassium. Tohoku J. Exper. Med. 85:181, 1965.
13. Mendlowitz, M., Torosdag, A., and Sharney, S.: The force and work of digital arteriolar vasoconstriction in hypertension. J. Appl. Physiol. 10:136, 1957.
14. Mendlowitz, M.: The digital circulation, New York, 1954, Grune & Stratton, Inc.
15. Mendlowitz, M., and Naftchi, N.: Work of digital vasoconstriction produced by infused norepinephrine in primary hypertension, J. Appl. Physiol. 13:247, 1958.
16. Ford, R. V., Moyer, J. H., Handley, C., and Spurr, C. L.: Chlorothiazide (diuril): orally effective nonmercurial diuretic agent, Med. Rec. Ann. 51:376, 1957.
17. Tapia, F. A., Dustan, H. P., Schneckloth, R. A., Corcoran, A. C., and Page, I. H.: Enhanced effectiveness of ganglion-blocking agents in hypertensive patients during administration of saluretic agent (Chlorothiazide), Lancet 2:831, 1957.
18. Hollander, W., and Wilkins, R. W.: Chlorothiazide: new type of drug for the treatment of arterial hypertension, Boston Med. Quart. 8:69, 1957.
19. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (diuril): Its use alone and combined with other antihypertensive agents, J.A.M.A. 166:137, 1958.

Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure

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Although the hemodynamic effects of hypovolemia and vasodepressor syncope have been studied extensively, the results have often been equivocal and inconsistent. This has been due in large part to differences in experimental design and measurement techniques and variable environmental and test conditions. One of the major technical problems has been the lack of a generally satisfactory method for depleting the effective blood volume. Recently, the application of negative pressure to the lower body (LBNP) has been shown to be a reproducible and effective means for sequestering blood from the central circulation at variable rates and in various amounts, and for the consistent induction of vasodepressor syncope. This study was undertaken to evaluate the hemodynamic responses and the adaptive mechanisms of human subjects to progressive hypovolemia proceeding to syncope by using a regimen of graded degrees of LBNP with controlled environmental and test conditions.

Methods

Seven experienced healthy male volunteers, familiar with LBNP exposures and vascular catheterization, were selected as subjects. Their average physical characteristics are as follows (mean [range]): age 30 years (25 to 40); weight 73 kilograms (59 to 96); surface area 1.86 sq. M. (1.66 to 2.18). None had a history of fainting except for one subject who had fainted twice and approached fainting twice during emotional stresses over the past several years. He denied any orthostatic symptoms and had been found to respond normally to head-up tilting.

The chamber is a steel cylinder closed at one end. The subject lies supine in the

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chamber on a foam rubber mattress straddling a narrow padded saddle which provided support during the suction exposures. The open end of the chamber was sealed at the subject's waist with a baffle-plate and a cylindrical polyethylene sheet one end of which was tied over the end of the cylinder the other carefully folded and tucked into the orifice between the subject's waist and the baffle plate Graded degrees of negative (subatmospheric) pressure were provided by variably venting the output of a commercial vacuum cleaner Chamber temperature and pressure were measured with an indwelling thermometer and a mercury manometer Graded decrements of pressure were used to provide a series of steady-state conditions during progressive hypovolemia Ten minute exposure periods were chosen because earlier studies with this device showed that cardiovascular responses are essentially complete within 5 minutes of a change in the chamber pressure The term syncope is used to denote the conglomeration of symptoms and signs that precede loss of consciousness it is not restricted to those instances in which consciousness was actually lost.

Polyethylene catheters (I D 1 1 mm) were passed into an adjacent right antecubital vein and artery in each subject before each test by a percutaneous technique modified after Seldinger The tip of the 40-cm long arterial catheter was placed in the subclavian artery and under fluoroscopic control the tip of the 70-cm long venous catheter was placed in the superior vena cava In one subject the venous catheter could not be placed properly so central venous pressure (CVP) and cardiac output (CO) measurements could not be carried out during this study The external ends of the catheters were connected to stop-cock manifolds permitting rapid sequential measurement of pressures, injection of dye, aspiration of blood samples, and flushing (with a dilute solution of heparin in-saline) Electrocardiographic (ECG) electrodes were placed on each extremity a venous occlusion cuff (15 cm in width) on the left upper arm and mercury in silastic girth gauges on the left forearm (for

Table I Hemodynamic effects of hypovolemia and syncope

	Control	4 subjects—all conditions				
		Chamber pressure				
		−10 mm. Hg	−20 mm. Hg	−30 mm. Hg	−40 mm. Hg	−50 mm. Hg
Heart rate	[illegible](5.8)	61(3.6)	67(7.6)	70(7.8)*	79(10.4)*	90(16.9)*
Systolic blood pressure (mm. Hg)	125(13.3)	126(13.8)	124(14.8)	125(11.0)	122(9.7)	110(8.8)
Diastolic blood pressure (mm. Hg)	71(9.2)	72(10.7)	71(9.4)	70(3.3)	70(6.8)	61(7.0)
Mean blood pressure (mm. Hg)	91(12.7)	94(10.0)	93(11.7)	92(8.0)	85(3.3)	80(9.5)
Central venous pressure (mm. Hg)	5.2(2.0)	1.1(2.6)	0.6(2.4)	−1.4(2.4)*	−2.5(3.5)*	−3.4(2.3)*
Cardiac output (L./min.)	4.9(0.5)	4.8(0.5)	4.5(0.8)	4.2(0.6)	3.9(0.5)*	3.4(0.4)*
Stroke volume (ml.)	84(11.9)	75(13.3)	67(16.0)*	61(13.2)*	53(14.6)*	39(9.2)*
Central blood volume (ml.)	1,4[illegible](267)	1,305(203)	1,295(240)*	1,140(257)*	1,170(313)*	1,000(163)*
Systemic vascular resistance (dyne-sec.-cm.⁻⁵)	1,418(245)	1,570(316)	1,640(298)	1,775(179)	1,990(173)*	2,290(283)*
Systolic ejection period (sec.)	0.291(0.014)	0.283(0.031)	0.260(0.024)	0.261(0.023)	0.234(0.033)*	0.217(0.028)*
Systolic ejection rate (ml./sec.)	276(25)	266(20)	253(37)	233(34)	225(41)*	174(21)*
Stroke work (gram-meters)	130(18.5)	114(11.8)	95(17.6)	82(16.4)*	74(19)*	53(11.9)
Forearm blood flow (ml./100 ml./min.)	8.2(2.73)	8.25(1.66)	6.45(1.46)	3.75(2.4)	4.45(2.16)	6.45(7.8)
Forearm vascular resistance (units)	21.9(13.9)	17.1(8.3)	18.9(9.3)	23.2(13.5)	27.2(16.1)	21.7(11.5)

Values are means (standard deviation)
*Denotes significantly different changes from control values ($p < 0.05$)

plethysmography) and across the chest (for respirometry) The ECG and respirometry tracings, arterial and venous blood pressures, and the indicator-dilution curve were displayed on an oscilloscope and recorded on a multi-channel photographic recorder Blood pressures were measured by means of Statham (P23 Db) pressure gauges mean pressures were obtained electronically Zero-reference for the gauges was set at the mid-chest level All pressure recordings for analysis were made at a paper speed of 50 mm per second Blood pressure heart rate (HR) and respiration rate measurements were taken from the recordings just before the dye curve inscriptions values over a full respiratory cycle were averaged and this average represents the sample period Fry s study indicates that such a catheter pressure gauge system has an essentially uniform frequency response to approximately 10 Hz (c.p.s.) Although errors due to acceleration transients and volume changes of the catheter certainly were significant the measurements of systolic, diastolic, and mean pressures delineation of systolic ejection and diastolic filling periods, and the estimation of mean systolic arterial pressure seemed acceptably accurate. Lead II of the ECG was monitored throughout each experiment for changes in rate rhythm and conduction and P QRS and T pattern changes Although phasic CVP patterns were recorded only mean values are presented End-diastolic pressure measurements were found to be less reliable and often difficult to measure accurately where they could be measured with accuracy the values were similar to the mean values but slightly greater

CO was measured by the indicator-dilution technique using an injectate of 5 mg of indocyanine green dye which was flushed from the catheter with approximately 5 ml. of saline Arterial blood was withdrawn at the rate of 25 ml per minute through a cuvette densitometer by a constant speed pump Stroke volume (SV) was calculated by dividing CO by HR and central blood volume (CBV) was taken as the product of CO and mean transit time Systemic vascular resistance (SVR) was derived as the

−40 mm. Hg (syncope)	Early recovery	Late recovery	7 subjects, 5 selected conditions				
			Control	Full compensation	Syncope	Early recovery	Late recovery
64(20.5)	81(3.3)	86(8.3)	69(5.7)	80(18.2)*	65(18.8)	54(8.1)	59(7.2)
75(21.1)*	115(21.8)	124(5.7)	122(11.1)	112(12.0)	75(15.6)	104(25.0	117(15..)
47(21.1)*	64(7.0)	71(4.4)	69(9.7)	73(12.7)	43(20.3)	87(17.2)*	66(13.8)
54(21.7)*	87(10.1)	91(5.0)	89(10.3)	83(18.0)	55(18.8)*	79(20.6)	87(15.8)
2.0(2.5)*	6.9(2.4)	6.9(2.4)	6.2(1.8)	−2.0(3.0)	0.8(4.2)*	6.1(1.9)	6.5(1.9)
−3/0.7)*	4.6(9.6)	4.4(0.8)	5.1(0.6)	3.3(0.6)*	2.6(0.7)*	5.2(1.7)	5.8(1.3)
37(7.3)*	97(23.7)	94(18.4)	85(9.6)	40(5.2)*	37(7.4)	97(22.2)	96(18.0)
610(135)*	1,430(257)	1,565(205)	1,338(200)	850(160)*	780(403)*	1,410(250)	1,333(329)
2,018(366)*	1,443(467)	1,270(181)	1,560(347)	2,230(327)*	2,000(390)	1,470(264)	1,430(205)
0.257(0.040)	298(0.015)	0.207(0.035)	0.301(0.021)	0.225(0.025)*	0.264(0.061)*	0.305(0.027)	0.313(0.032)
167(35)*	822(100	302(111)	291(82.8)	178(15.8)*	132(29.0)*	820(93.1)	310(41.5)
34(12.0	132(87.2)	134(11.2)	117(16.1)	81(8.0)*	32(11.8)*	1..1(46.8)	137(18.6)
4.9(1.61)	6.45(2.81)	7.5(3.52)	5.07(2.13)	6.03(2.63)	5.8(1.33)	8.33(1.47)	9.2(3.62)
14.2(6.7)	18.9(5.1)	12.8(6.4)	21.0(10.7)	20.8(8.05)	10.5(3.13)	14.2(7.9)	11.8(3.43)

product of the quantities (mean arterial blood pressure minus CVP) and (79.9) divided by CO. The systolic ejection rate is taken as the ratio of SV to systolic ejection period (SEP). The product of mean systolic arterial blood pressure and SV represents stroke work (SW). Respiration rate was determined from the chest girth gauge recordings.

Changes in forearm blood flow were estimated by venous occlusion plethysmography with a cuff occlusion pressure of 45 mm Hg[3] girth gauges were adjusted to a tension of 20 g. Because of the artifacts introduced by distal arterial occlusion, an occlusive wrist cuff was not used. Forearm vascular resistance was calculated as the ratio of mean arterial blood pressure to forearm blood flow and is expressed in units of resistance.

Room temperature remained relatively constant throughout this series of experiments, varying between 21.1 and 25.5° C. Chamber temperature rose during each experiment to peak levels between 28.0 and 29.1° C.

Because syncopal symptoms developed at various intervals after the onset of LBNP exposures and thus at different chamber pressure levels, the data were analyzed in 2 ways. *A*. By comparing all subjects under 5 conditions: (1) control following instrumentation and 60 minutes of recumbency; (2) at full compensation, the measurement just before the onset of syncope; (3) at syncope when advanced syncopal symptoms and signs were well established; (4) early recovery (R 1) immediately following restoration of chamber pressure to the ambient level; (5) late recovery (R 2) 10 minutes after the restoration of chamber pressure. *B*. Because 4 of the subjects reached syncope at the same stress level (−60 mm Hg), their data were compared for each of the 6 stress periods as well as during control and recovery. These data are presented in Table I and Figs. 1 and 2. Because CVP values fell below zero during most exposures, calculation of per cent change was made by comparing individual changes with the maximum change from control value.

The statistical significance of these data was determined by using analysis of variance to evaluate main effects and the interactions of subjects, conditions, and time. When the probability of the F values for main effects of conditions was 0.05 or less, the significance of the differences among the 5 or 9 conditions was tested using Student's t test with correlated means; significant p-values ($p < 0.05$) are denoted in the table by an asterisk.

Procedure

Each subject fasted and abstained from smoking and unusual exercise for 10 hours before the morning test. Five hundred milliliters of water was drunk 2 hours before arrival at the laboratory. Vascular catheters were placed with sterile technique under local anesthesia and the subject walked to the adjacent test room where he remained recumbent in the LBNP chamber for 60 minutes prior to the application of negative pressure. During this time, he was instrumented with ECG electrodes, girth gauges on the arm and chest, and a venous occlusion cuff, and catheter connections and calibrations were carried out. Five minutes before the onset of the suction, control recordings were obtained for heart and respiration rates, arterial and venous pressures, CO, and forearm blood flow. After the completion of these control recordings and blood sampling, chamber pressure was changed to −10 mm Hg (10 mm Hg below the ambient atmospheric level), maintained there for 10 minutes and lowered to −20 mm Hg for 10 minutes. Thereafter chamber pressure was changed in 10 mm decrements every 10 minutes until syncope occurred, when chamber pressure was restored to the atmospheric level over a period of approximately 1 minute. Replicate sequences of recordings were carried out during the last 4 minutes of each 10-minute period of negative pressure exposure, when syncope developed, immediately after the restoration of chamber pressure, and 10 minutes later. Following the test procedure, the catheters were removed, the subject observed for 90 minutes and discharged.

Intrathoracic pressure changes. In order to estimate the effect of LBNP on intrathoracic pressure and thus cardiac filling pressure, another series of tests was carried out in a different group of 6 similar subjects. A thin latex esophageal balloon 10 cm in

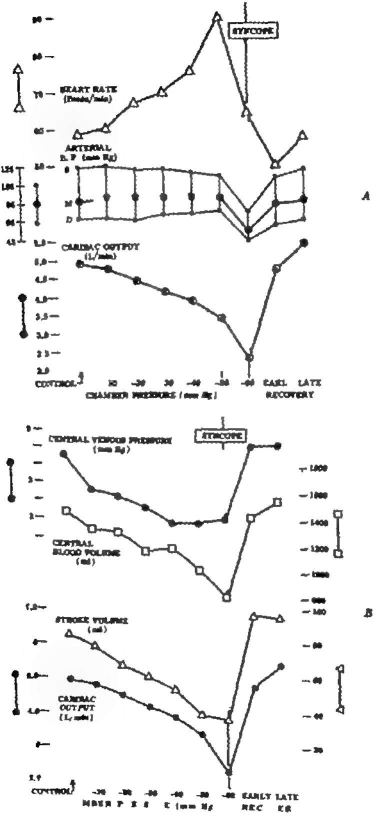

Fig. 1. Circulatory changes during exposures to LBNP through −60 mm Hg and recovery: mean values for 4 subjects. A, Serial changes in heart rate, arterial blood pressure and cardiac output. Abbreviations S, M and D represent systolic, mean, and diastolic blood pressure. B, Changes in selected correlates of ventricular [illegible] tion.

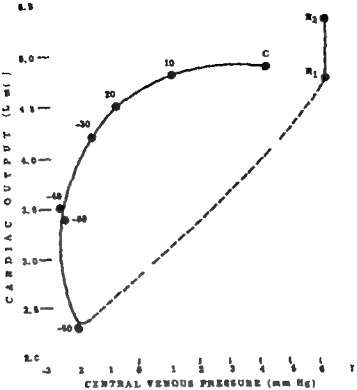

Fig 2 Relationship between cent l enous pressure nd cardiac output d ring graded exposures to LBNP Numbers adjacent to data points represent chamber pressure t the time of measurement, and C R 1 and R-2 represent control conditions and early and lat recovery Dotted l ne denotes pid change chamber pressure from −60 mm Hg to the mbient level

length was attached to a catheter and placed under fluoroscopic control into the lower third of the esophagus. Pressure re cordings were carried out through several normal respiratory cycles at ambient at mospheric pressure and during exposures to graded LBNP levels through −60 mm Hg Measurement of mean pressure and pressure changes during respiration were made at each test period and following return to control conditions.

Results

Except for moderate local sensations of saddle pressure and a mild fullness in the lower abdomen and legs there were usually no significant symptoms throughout the negative pressure exposures until the onset of syncope. A few subjects developed mild very transient presyncopal symptoms and transient changes in the HR and arterial pressure immediately after chamber pressure changes at higher levels of suction However at syncope significant symptoms and signs came on abruptly and progressed inexorably and quickly to a new relatively stable hemodynamic state between good compensation and circulatory collapse This state of vasodepression persisted long enough in 6 of the subjects to permit physiological recordings and blood sampling before unconsciousness (at least 3 minutes) One subject progressed from first symptoms to sinus arrest in 5 seconds, and to unconsciousness in 20 seconds so that data at this point could not be obtained in this subject Sinus arrest persisted for 9 seconds and unconsciousness lasted about 20 seconds. Nodal rhythm followed the sinus arrest and was superseded in 10 seconds by sinus bradycardia which persisted until completion of the test. Syncopal symptoms varied among the individual subjects but usually included yawning sighing restlessness malaise and anxiety weakness, sweating abdominal discomfort and nausea.

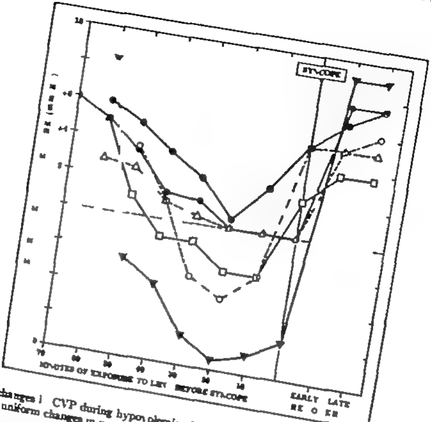

Fig. 3 Individual changes in CVP during hypovolemia. Abscissal values are arranged as time prior to syncope to demonstrate the uniform changes in pattern of CVP response as syncope is approached.

Each subject recovered quickly from the symptoms and felt well within 30 minutes after the test. The subject with a history of syncope proved least tolerant to LBNP fainting at a negative pressure level of −30 mm Hg.

Control values for the hemodynamic variables and parameters presented are normal for experienced recumbent subjects in this laboratory. Table I contains the mean values (± S.D.) for the 7 subjects under the 5 conditions chosen for comparison. Table I and Fig. 1 contain mean values for the 4 subjects who fainted at the −60 mm Hg level at each of the grades of negative pressure exposure as well as during the control and recovery periods. During the milder degrees of suction (−10 and −20 mm Hg) there were nonsignificant and inconsistent changes in all the *measured* variables except for CVP which fell immediately uniformly and consistently and continued falling along with chamber pressure decrements until test periods before syncope. At this point CVP began rising in 4 of the subjects and leveled off in the other 2 (Fig. 3). As is the case with most studies of hypovolemia, HR was slow to change but once started it continued rising throughout the LBNP exposures until syncope when it fell abruptly. HR rise was never great and maximal heart rate exceeded 100 beats per minute in only 2 subjects. Mean blood pressure was maintained very near control levels throughout the period of cardiovascular compensation while pulse pressure gradually narrowed due to both rising diastolic and falling systolic pressures. Although forearm blood flow changes were variable there was a tendency for a fall in flow during the period of compensation systemic vascular resistance rose relatively quickly and continued rising during compensation. Fig. 1B shows the similar early changes in CO (which can be taken as equivalent to venous return under these relatively stable hemodynamic conditions), CBV, SV, and CVP followed by a later rise in CVP in the face of a continued decline in the values of the other factors. SEP changes were comparable up to syncope, when they rose significantly due

apparently to the change in HR when these values are corrected for HR variations (ejection time index) they show no important change through the early periods of hypovolemia but a moderate fall later which persisted during syncope.

The onset of syncope was always sudden and usually abrupt. In a few cases where satisfactory recordings were made during this period a slight blood pressure fall preceded bradycardia by a few seconds. With the fall in blood pressure (systolic, diastolic, mean, and pulse pressure) and HR, CVP rose, CBV, CO, and SER continued falling, reaching near 50 per cent of control levels, and SV remained near the previous very low value. Although forearm flow fell in the group of 4 subjects who fainted at −60 mm. Hg, this was not the case when the entire group was considered, nor were changes in vascular resistance significant. It is possible that the use of 45 mm. Hg for venous occlusion pressure during plethysmography caused erroneously low blood flow values in those subjects with very low arterial blood pressure at syncope. However, an increase in blood flow was not noted at syncope in those subjects with blood pressures above this level, and in many other studies of syncope a significant increase in forearm blood flow has never been observed, regardless of blood pressure levels at syncope. Respiratory rates varied slightly and inconsistently; significant tachypnea was never observed nor were there subjective or objective evidences of hyperventilation. However, unpublished studies of other subjects showed that a mild degree of hyperventilation occasionally occurs during advanced hypovolemia and at syncope.

During restoration of chamber pressure toward the atmospheric level, obvious improvement in symptoms and in the hemodynamic state was apparent within 30 seconds and marked improvement within 1 minute. During the recovery period HR remained low and respiratory sinus arrhythmia was often pronounced. While other variables and parameters returned to or near baseline levels, CVP, CO, CBV, and SV rose to values above their control levels, although the changes are not statistically significant.

In 4 subjects there were no important ECG changes during any of the exposure periods. As described above, one subject developed sinus arrest within 5 seconds after the onset of syncopal symptoms, and in 2 others a nodal pacemaker supervened transiently during sinus bradycardia during the restoration of chamber pressure as the sequestered blood was translocated from the caudal veins to the central circulation.

During vasodepressor syncope the hemodynamic condition was unexpectedly stable for a period of at least 3 minutes in the 6 subjects in whom measurements could be made at all, so that CO measurements here are probably quite accurate. But HR and blood pressure measurements made during the early recovery period immediately after the restoration of chamber pressure were relatively unstable so that hemodynamic measurements at this time must be considered semi-quantitative.

As has been demonstrated with other circulatory stresses,* CBV determinations are subject to error during periods of altered blood flow distribution when arterial samples are obtained from a peripheral site. Since it seems certain that blood flow distribution was disturbed during the later periods of these LBNP exposures and in the early recovery period, and since the subclavian artery was the sampling site, CBV calculated for these periods are of uncertain validity.

During the secondary series of LBNP exposures carried out to estimate intrathoracic pressure changes, esophageal pressure did not change significantly in 3 subjects and fell slightly in the other 3, but never more than 2.2 mm. Hg even at chamber pressure levels of −60 mm. Hg. Pressure changes during respiration varied but tended to diminish slightly at lower chamber pressure levels. It seems unlikely, therefore, that changes in intrathoracic pressure played a significant part in altering cardiac filling pressures.

Discussion

Many techniques have been used in the laboratory to diminish the effective blood volume and induce vasodepressor syncope.

*The portion of the total blood volume which is actually in currency and available to the heart for active circulation.

bleeding, peripheral pooling of blood with venous occlusion cuffs and vena cava obstruction by intracaval balloons, accelerative forces (tilting and centrifugation), positive pressure breathing, or a combination of these devices. Often vasodepressive drugs, such as nitrites, have been used as adjuvants to exaggerate the circulatory strain. The use of LBNP as a device for producing hypovolemia and syncope offers several advantages: (1) It is comfortable and acceptable to the subjects; (2) the stress is quantifiable and reproducible; (3) the rate of production and degree of hypovolemia can be controlled readily; (4) syncope can always be induced without adjuvants; (5) impounded blood can be replaced whenever and as quickly as desired; (6) the effects of altered hydrostatic gradients are not a consideration; (7) once syncope ensues, most subjects linger in a relatively stable hemodynamic condition for a sufficient period to permit physiological testing; and (8) the equipment is inexpensive and can be made compact, lightweight, and portable.

The application of negative pressure to the body has a long history as a physiological stressor and treatment regimen. In 1834 Junod first presented his clinical experiences with the use of subatmospheric pressure applications. Hemospasia ("blood sucking") as it came to be called enjoyed great popularity and was used widely throughout Europe and America to treat a host of conditions and diseases, and to induce syncope which was used occasionally as surgical anesthesia. In recent years, there has been a renewed interest in the use of negative pressure applications in physiological research and clinical medicine and lately this interest has increased because of its proposed use as a conditioning device for the cardiovascular system during exposures to weightlessness.

It seems clear that the primary physiological effect of the application of negative pressure to the body is a diminished tissue pressure in the exposed region. Coles has demonstrated that decrements in pressure (up to 200 mm. Hg) in the chamber surrounding an extremity are transmitted to the tissues with very little attenuation at least to a depth of 2.5 cm. The consequent increased pressure difference across vessel walls brings about dilatation and pooling of blood especially in the compliant venous system and at the capillaries it promotes the filtration of fluid and the formation of edema. The extent of this pooling of blood and loss of fluid is primarily a function of the degree of suction applied and the duration of exposure; it is apparently little affected by ordinary changes in environmental or test conditions. Brown and associates using the technique of center-of-gravity shift to measure fluid displacement estimated that at least 10 g of blood per kilogram of body weight are translocated during lower body exposure to 70 mm. Hg suction for 1 minute. As she points out this certainly underestimates the actual fluid shift because of technical errors which cannot be controlled or measured. Musgrave measured plethysmographically the change in the volume of blood in both legs during 5 minutes of negative pressure exposure at 40 mm. Hg and found that an average of 614 ml. had been pooled. Estimates from bleeding studies suggest that over 25 per cent of the effective blood volume (or over 1,500 ml.) must be lost from normal experienced recumbent subjects before syncope can be induced consistently. Presumably the intense engorgement and vasodilatation produced in the exposed tissues influences the regional circulation by means of local vasomotor reflexes. It remains uncertain whether such local vascular stimuli affect the general circulation but this seems unlikely. Alexander has presented the only evidence that this might be the case.

CVP was consistently the first circulatory measurement reflecting hypovolemia. Exposures to even the mildest degrees of lower body suction brought about significant falls in CVP well before any meaningful changes in HR, blood pressure, or CO. This is similar to the experience with bleeding and the use of peripheral venous occlusion cuffs. Sauer and colleagues have suggested that the relationship between CVP and effective blood volume can be expressed by the statement: CVP changes by 0.49 ± 0.12 cm. of water per kilogram of body weight for each milliliter change in effective blood volume. Thus in considering the 4 subjects who fainted at −60 mm. Hg

their maximal mean CVP fall of 7.7 mm Hg would be attributed to an effective blood volume loss of 1,460 ml. The later rise in CVP in the face of decreasing venous return and CBV can be explained best by venoconstriction. Several investigators have demonstrated that the venous system behaves passively during hypovolemia unless and until the volume depletion becomes very severe: a loss of several hundred milliliters of blood is required to provoke a significant increase in venous tone.[6, 30-36] Although Gilbert and Stevens[36] did see changes in peripheral venous tone during LBNP exposures at −60 mm Hg, significant changes were not observed during exposures to lesser degrees of suction. Such an enhanced venous tone would be expected to redistribute blood from peripheral capacitance vessels into the central circulation, increasing venous return, CBV, SV, and CO, as seems to occur with exercise.[7,38] That this was not observed may be attributed to the relative weakness of the venoconstrictive response and the severe depletion of the circulating blood volume. Persisting venoconstrictive effects may account for the elevated values of CVP, SV, CBV, and CO during the recovery period. Although poststress plethora must also be considered, it seems more likely that the effective blood volume during recovery was still below control levels because recruitment of extravascular fluid from nonexposed regions was probably negligible and unreported leg girth measurements during this and other studies in this laboratory have shown that leg volume during recovery is significantly greater than during the control period, due apparently to persisting edema. Obviously, the venoconstriction observed during advanced hypovolemia and at syncope will disturb the usual relation between CVP and effective blood volume, so that CVP changes cannot be relied upon to reflect changes in effective blood volume and to determine treatment when volume depletion is severe.

Differing viewpoints concerning the relative importance of various possible determinants of heterometric autoregulation have been summarized recently.[8-41] In a pertinent study, de Freitas and associates[42] observed that during alterations in effective blood volume produced by infusions and the peripheral pooling of blood behind occlusion cuffs, there were no significant correlations among pulmonary blood volume, SV, and CO. He concluded, as have others, that ventricular filling pressure is the critical determinant of CO and that changes in various component portions of the CBV affect CO by altering atrial pressure. The data presented here indicate that this may not always be the case, that during advanced hypovolemia changes in filling pressure and CO may be divergent and that, at least under certain circumstances, the volume of blood in the "preventricular sumps," not filling pressure, may determine CO. Fig. 2 displays the relationship between CO and CVP for the 4 subjects who fainted at the −60 mm Hg level, demonstrating the large CVP and small CO changes during the early portion of the stress, the moderate changes in each during the midportion, and the later large fall in CO as CVP rises slightly. This CVP-CO divergence can also be seen in the data for the entire group of 7 subjects in Table I: between the time of full compensation and syncope, CVP rose 2.3 mm Hg while CO fell 0.9 L. per minute. There is now ample evidence that such divergence is not uncommon during changes in effective blood volume.[17, 33, 43-44] It has been suggested that the autonomic nervous system may alter this relationship by changing myocardial "tone" or contractility.[45, 4]

Fig. 1B exhibits the patterns of change of 4 factors which have been considered important correlates of heterometric autoregulation. It is apparent that, under these experimental conditions, CO (or venous return), SV, and CBV change similarly and differ from CVP changes during severe hypovolemia and syncope.

Throughout the LBNP exposures, forearm blood flow tended to fall slightly up to and through syncope but rose greatly during the recovery period, while forearm vascular resistance tended to rise during compensation and fall at syncope. This is similar to the findings of Weiss and coworkers[7] but differs from the findings of Barcroft and Brigden and their colleagues,[47, 4] who studied extremity blood flow in syncope induced by various meth-

ods. They usually found a significant increase in blood flow and a fall in vascular resistance with the onset of syncopal symptoms and suggested that syncope was due essentially to bleeding into the peripheral muscles. Different measurement techniques may have contributed to this discrepancy. An occlusive distal cuff was not included in these experiments in order to obviate the frequent and inconstant artifact caused by its use. The inclusion of the distal forearm and hand in the test region may have modified the blood flow response in our experiments. In any event these results are not as different as it first appears for in our study the sustained forearm blood flow at syncope in the face of the large fall in perfusion pressure implies that active vasodilatation of the resistance vessels had occurred.

Summary

To study the effects of graded hypovolemia and vasodepressor syncope 7 normal subjects were instrumented with arterial and venous catheters, ECG electrodes, chest and forearm girth gauges (for respiratory rate and plethysmography) and exposed to graded degrees of lower body negative pressure, proceeding to syncope. Hemodynamic responses were generally similar to hypovolemia induced by other means. HR and SVR rose, mean blood pressure remained unchanged, pulse pressure, CO, SV, CBV, SW, forearm blood flow and CVI fell when hypovolemia became severe. CVP rose. At syncope CVP rose further while HR, arterial pressures and SVR fell abruptly and CO continued falling; there was no significant change in forearm blood flow. All factors returned to or above control values in the recovery period. LBNP proved to be a reproducible effective and practical means to produce hypovolemia and induce vasodepressor syncope.

We should like to thank Mr. Robert Bachert and his staff for assistance with the statistical analyses.

Addendum

Since this paper was submitted for publication Epstein and associates reported that during vasovagal syncope there is dilatation in the forearm resistance vessels but venoconstriction.

REFERENCES

1. Fry, D. W., Noble, F. W., and Mallos, A. J.: An evaluation of modern pressure recording systems, Circulation Res. 5:40, 1957.
2. Egan, C. J.: The physics of the mercury strain gauge and of its use in digital plethysmography, USAF Tech. Note AAL TN-60-17, February 1961.
3. Graf, K.: Zur Methodik der venösen okklusions-Plethysmographie. Die Wirkung distaler Gefässokklusion auf die Durchblutung des Unterarms, Acta physiol. Scandinav. 60:70, 1964.
4. Weissler, A. M., Harris, L. C., and White, G. D.: Left ventricular ejection time index in man, J. Appl. Physiol. 18:919, 1963.
5. Marshall, R. J., and Shepherd, J. T.: Interpretation of changes in central blood volume and slope volume during exercise in man, J. Clin. Invest. 40:375, 1961.
6. McIntosh, H. D., Gleason, W. L., Miller, D. E., and Bacos, J. M.: A major pitfall in the interpretation of central blood volume, Circulation Res. 11:712, 1962.
7. Junod, V. T.: Recherches physiologiques et thérapeutiques sur les effects de la compression et de la raréfaction de l'air tant sur les corps que sur les membres isolés, Revue Med. Franc. et Étrang. vol III, 1834.
8. Junod, V. T.: Traité theorique et pratique de l'hemospasie, Paris, C. Masson, 1875.
9. Ficinus, R.: Die Hemospasie. Geschichte, Beschreibung and Wirkungen der Grossen Ventouren Junods oder des Schröpfstiefels, Leipzig, L. Voss, 1848.
10. Bier, A.: Hyperemia as a therapeutic agent (translated by C. M. Blech), Chicago, 1905, A. Robertson.
11. Wakamundeka, M. C.: Pneumatic therapy (Junod hemospasia) (Bier hyperemia), New York, 1936, B. Lust.
12. Yamada, S., and Burton, A. C.: Effect of reduced tissue pressure on blood flow of the fingers; the veni-vasomotor reflex, J. Appl. Physiol. 6:501, 1954.
13. Greenfield, A. D. M., and Patterson, G. C.: Reactions of the blood vessels of the human forearm to increases in transmural pressure, J. Physiol. 125:508, 1954.
14. Greenfield, A. D. M., and Patterson, G. C.: On the capacity and distensibility of the blood vessels of the human forearm, J. Physiol. 131:290, 1956.
15. Coles, D. R., Kidd, B. S. L., and Patterson, G. C.: The reactions of the blood vessels of the human calf to increases in transmural pressure, J. Physiol. 134:665, 1956.
16. Coles, D. R., and Patterson, G. C.: The capacity and distensibility of the blood vessels of the human hand, J. Physiol. 135:163, 1957.
17. Coles, D. R.: Heat elimination from the toes during exposure of the foot to subatmospheric pressures, J. Physiol. 135:171, 1957.
18. Crossley, R. J., Greenfield, A. D. M., Plassaras, G. C., and Stephens, D.: The interrelation of thermo-regulatory and baroreceptor reflexes in

the cont ol of the blood vessels in the human forearm J Ph siol 183:628, 1966

19 G yton A C Pr ther J Schul, K nd Mc Gehee J Interstitial fluid pressure. IV It effect on fl id movement through the capillary w ll, Circulation Res 19 1022 1967

20 Restall, P A and Smirk, F H Variations in blood pressure nduced by hexamethonium bromide n conjunction with postur and negat ve pressures pplied t the body surface Proc. Univ Otago Medical School 29 10, 1952

1 Restall P A and Smirk, F H Regulation of blood pressure level by hexamethon um bromide and mecha ical devices Brit. Heart J 14 1 1952

22 Saunders, J S Neg t ve pressure device for ontrolled hypotension dur ng urgical opera tions, Lancet 1 1 1952

23 Sa nders, J Effect of cont olled hypot nsion on erebr l function and cir ulation, Lancet 1 1156 1954

24 Heyns O S U e of abdominal decompression in pregnancy nd labor to improve fetal oxygen tion Develop Med Child Neurol 4:473 1962

25 Murray R Krog J Ca bon L and Bowers, J Lower bod negative pressure as provoca tive test for the circulatory system Physiologist 8:238, 1965 (abst)

26 Murray R Krog J Carlson L nd Bowers J Responses t lower body neg tive pressure following exposure to de-conditioning environments, Clin. Res 13 401 1965 (abstr)

27 Samueloff S B owse N L, nd Shepherd J T Response of pacity essels human limbs t head-up tilting nd pplication of ue tion t lower body Physiol 8:265 1965

28 Sears W J nd Meehan, J I Effect of lower body negative pressur on centr l enous pressure venou tone and heart t Fed Proc 25:393 1966

29 Steven P M d Laml L E Effects of lower bod neg tiv pressur on the cardiovascular stem Am J Cardiol 16:500, 1965

30 Zechma F W M rgan F S Mams, R C nd C ib J C Respir tory mechanics and pulmonar diff sing capacity th lower body negative pressure, J Appl Physiol. 22:247 1967

31 Sha D B C Kotas, F nd Thompson M L Syncope induced by pplication of negative pressure t the lower body nd its effect on lung CO diffusing capacity Aerospace Med. 37 154 1966

3. Murra R Cumulative effects of venesection and lower bod negative pressure Aerospace Med. 38:243 1967

33. Piemme, T McCally M nd Murray R. Renal responses t lower body negative pressure Tech ic l report, AMRL — TR 66-39 USAF 1966

34 Coles, D R Meas rement of extra vascular tissue pressure during local exposur to subatmospheric pressure (Thesis)

35. Coles, D R Kidd, B S. L, and Moff t W Distensibility of blood vessels of the huma calf determined by local application of subatmospheric pressures, J Appl Physiol. 10:461 1957

36. Brown, E, Goel, J S. Greenfield, A. D M and Plassaras, G C. Circulatory responses to simulated gravitational shift of blood in man induced by exposure of the body below the iliac crests to subatmospheric pressure J Physiol. 183:607 1966

37 Musgrave S.: Thesis, University of Kentucky 1967

38 Wallace, J and Sharpey Schafer E. P: Blood pressure changes following controlled hemorrhage in man, Lancet 2:393, 1941

39 Barcroft H Edholm, O G McMichael, J and Sharpey Schafer E. I Posthaemorrhagic fainting Lancet 1:489 1944

40. Barcroft H and Edholm O G O the vasodilatation in skeletal muscle during post haemorrhagic fainting, J Physiol. (London) 104 161 1945

41 Green D M., and Methany D The estimation of acute blood loss by the tilt test, Surg Gynec. & Obstet. 81 1015 1947

42 Gaskill, I and Burton, A C. Local postural vasomotor reflexes arising from the limb veins, Circulation Res. 1:27 1953

43 Wallis, W Brenman, R., and Honig, C. R.: A venus venomotor response to local congestion, J Appl Physiol. 18:533 1963

44 Alexander R. S Reflex alterations in venomotor tone produced by venous congestion, Circulation Res 4:49 1956

45 Gauer O H Henry J P nd Sieker H O: Changes in central venous pressure after moderate hemorrhage and transfusion i man, Circulation Res 4 79 1956

46. Henry J P Gauer O and Sieker H. O The effect of moderat changes in blood vol me on left nd right atrial pressures, Circulation Res. 4:91 1956

47 Warren, J V Brannon, E. S., Stead, E A., and Merrill, A J The effect of venesection and the pooling of blood in the extremities on the trial pressure and cardiac output in normal subjects w th observations on acut circulatory collapse in three instances, J Cli I vest 24:337 1945.

48. Loutit, J F Millison, M D and Van der Walt, E. D V nous pressure during venesection and blood transfusion, Brit. M J 2:658, 1942.

49 Anderson D Physiology of central venous pressure i acut bleed ng Nordisk Med. 74:826 1965

50. Wood, E., and Eckstein, J S A tandem forearm plethysmograph for study of acute responses of the peripheral eins of man. The effect of nvironmental and local temperature changes and the effect of pooling blood in the extremities, J Clin. Invest. 37 11 1958.

51 Sharpey Schafer E. P Venous tone Brit M J 2:5267 1961

52. Shepherd, J T Role of the veins in the circulation, Circulation 33:484 1966

53 Pabst K., and Gauer O H: Nierenhämodynamik nd Ausscheidungsfunktion der iere unter differenten nderungen des Blut Volumens, Arch Physiol. 274:213 1961

54. Gauer O. H and Thron, H L. Properties of veins in vivo Integrated effects of their smooth muscle Physiol. Rev (Suppl 5) 42:283 1962.
55 Goel, S L., Pinter R. B and Arndt, J O Die Druckvolumen Charakteristik des Gesamtkreislaufes wacher Hunde nach schnellen Änderungen des Blutvolumens, Arch Physiol. 289 R92, 1966
56. Gilbert, C A and Stevens, P M Forearm vascular responses to lower body negative pressure, J Appl. Physiol. 21 1263 1966.
57 Wang, Y Blomquist G Rowell, L. B and Taylor H L. Central blood volume during upright exercise in normal subjects, Fed Proc. 21 124 1962.
58. Bevegård, B. S and Shepherd, J T Changes in tone of limb veins during supine exercise J Appl. Physiol. 20 1 1965
59 Guyton, A C. Venous return in Handbook of Physiol sect. 2 Circulation vol II chap. 32 1965
60. Sarnoff S J and Mitchell, J H The control of the function of the heart, Handbook of Physiol sect 2, Circulation vol I chap. 15
61. Braunwald, E. The control of ventricular function in man, Brit. Heart J 27 1 1965
62. de Freitas, F M Faraco, E. Z deAzevedo, D F Zachduchliver J and Lewin, L Behavior of normal pulmonary circulation during changes in total blood volume in man, J Clin Invest. 44:366 1965.
63. Warren, J V Weissler A M and Leonard, J J Observations on the determinants of cardiac output, Trans. Assoc. Amer Phys. 70 268 1957
64 Frye R. L and Braunwald, E Studies on Starling Law of the Heart. I The circulatory response to acute hypervolemia and its modification by ganglionic blockade J Clin Invest. 39 1043 1960.
65 Sjostrand, T The regulation of the blood distribution in man, Acta physiol. Scandinav 26:312, 1952
66 Warren, J V Brannon, E. S Weens, H S., and Stead, F A Effect of increasing the blood volume and right atrial pressure on the circulation of normal subjects by intravenous infusions, Am J Med. 4 193, 1948.
67 Fleming J W and Bloom W L Further observations on the hemodynamic effect of plasma volume expansion by Dextran, J Clin Invest. 36 1233 1957
68 Rushmer R F and Smith, D A. Cardiac control Physiol Rev 39:41 1959
69 Katz L N Analysis of the several factors regulating the performance of the heart, Physiol. Rev 35:91 1955
70. Weiss, S., Wilkins R W and Haynes, F W The nature of circulatory collapse induced by sodium nitrite J Clin Invest. 3? 73 1937
71 Brigden, W Howarth, S and Sharpey Schafer E P Postural changes in the peripheral blood flow of normal subjects with observations on vasovagal fainting reactions as a result of tilting, the lordotic posture pregnancy and spinal anesthesia, Clin. Sc 9 79 1950
72 Epstein, S. E Stampfer M and Beiser G. D Role of the capacitance and resistance vessels in vasovagal syncope Circulation 3?:524 1968.

Case reports

Surgical ligation of an anomalous left coronary artery arising from the pulmonary artery in an adult

Report of a case and review of the literature

Gerald I Summer M D
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Origin of the left coronary artery from the pulmon ary artery in individuals 16 years of age or more has been reported in 20 patients of whom only 5 were diagnosed during life One[3] underwent successful ligation of the anomalous left coronary artery only to develop post operative electrocardiographic changes sug gestive of severe my ocardial ischemia The adverse electrocardiographic changes in this patient weighed heavily in the decision to postpone surgery in the case of a 29 year old woman reported by Likar and associ ates

There is some questi on as t whether all cases in the older age group of anomalous left coronary artery should be electively surgically ligated To contribute t the experience needed t solve this therapeutic problem the following is a case report of this malformation in an adult who de veloped postoperative electrocardiographic changes without apparent ill effect after 20 months foll w up

Case report

An asymptomatic year-old man as adm tted to the Medical College of South Carolina H spital for diagnostic ev luat n because of heart murmur suggestive of aortic insufficiency and an abnormal electrocardiogram (ECG). He was first told of the heart murm hen he was rejected by the Selec tive Service S stem at the ge of 18 years There had been no sig ificant symptom or prior illnesses.

H ppeared well developed nd healthy with blood pressure of 110 systolic and 80 diastolic. The enou nd arterial pulses ere normal. Remarkable physical findings included continuou m rmu of Grade 2/6 intensity heard best t the third and fourth intercostal paces long the left sternal border There was lso Grade 1/6 soft blowing tolic murmur at the apex. A thrill as not pres ent. The emainder of the physical examination not remarkable. The ECG as suggesti of left entricular hypertrophy ith diastolic overload pattern (Fig 1). The chest x-r y revealed light cardiac dilatation with normal l ng fields

Cardiac catheterization performed on March 10 1965 A significant (18 per cent) ncrease in oxygen sat tion at the pulmonary artery level was noted as compared t the right entricle The pulmonary blood flow calculated t 3 times ystemic blood flow Indicator-d l tion curves were charac teristic of the left-to-right sh t, nd an injection t the aortic root showed an early ppearance time n sampling at the pulmonary artery Cineangio cardiographic tudies ith first i jection intr the left entricle and the second inject n i to the aorta just abov the aortic l showed grossly enlarged and tortuou right coronary artery ith opacification of the mai pulmonary artery The patient digitalized because of an increase in left entricular end-diastolic pressure t 15 mm Hg t rest.

F om the Department of Medicine (Cardiology) Medical College Hospital, Medical College of South Carolina, Charles ton S C
Received for publication Act. 30, 1967
*Cardiac catheterization was performed by Dr Charles P Summerall, III, Medical College Hospital, Charleston, S C

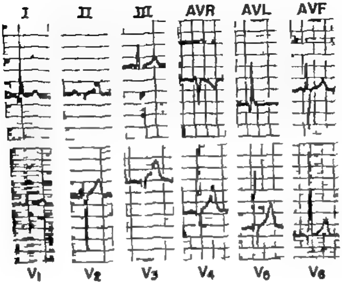

Fig. 1. ECG dated March 9, 1965, prior to diagnosis, which is suggestive of left ventricular hypertrophy.

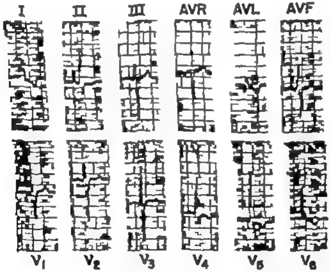

Fig. 2. ECG one month postoperatively showing left ventricular hypertrophy and *digitalis effect*.

On Aug. 6, 1965, surgery* was performed. The right coronary artery was greatly enlarged and tortuous. The origin of the left coronary artery was identified in the pulmonary artery. It was ligated for a distance of about 0.5 cm. from its orifice. The pressure in the left coronary artery was 50 mm. Hg prior to ligation and rose to 100 mm. Hg after ligation. The patient tolerated the procedure well and was discharged asymptomatic on Aug. 14, 1965.

One month later he was readmitted to the hospital because of dyspnea, pleuritic chest pain, increased cardiomegaly, and an oral temperature of 101° F. ECG (Fig. 2) were compatible with left ventricular hypertrophy and digitalis effect. He was considered to have postcardiotomy syndrome and treated 5 days with indomethacin and discharged asymptomatic on Sept. 30, 1965.

During follow-up examination a Grade 1/6 apical systolic murmur has persisted. However, he has

*Surgery was performed [redacted] Dr. William H. Lee, Department of Surgery, Medical College Hospital, Charleston, S. C.

remained asymptomatic while on no medication lead g actr. II A chest x-ray in December 1965 was normal

Discussion

It is not the purpose of this report to discuss the entire subject of anomalous left coronary artery but to emphasize some aspects of this disorder in adults. However a brief description of this disorder in infants and adults is needed to clarify presently employed terminology.

Anomalous left coronary artery arising from the pulmonary artery in the older age group is an unusual manifestation of congenital heart disease. Infants with this malady show no murmur but marked cardiomegaly with congestive heart failure and death from myocardial infarction usually occurs during the first year of life. Gouley divided this malformation into infantile and adult types. The adult type is usually asymptomatic, demonstrates a continuous murmur and mild left ventricular hypertrophy. As concisely outlined by Talner and co-workers[3] the development of a rich collateral coronary circulation permits survival into adulthood. Agustsson and colleagues[7] described 3 patients below 7 years of age with adult type of anomaly. They emphasized that the term "infantile" should be used to denote not the age of the patient but the presence of inadequate collateral circulation with supporting clinical and laboratory findings associated with it. To add further to the importance of correct interpretation of the terminology, Likar and associates presented their 39-year-old patient with a demonstrable anterolateral infarction, tachycardia and exercise intolerance. This patient clearly shows symptoms of the "infantile form" of the disease. Other communications[2] have described the broad clinical spectrum that exists in this malformation.

Our patient presented as the "adult" form of anomalous origin of the left coronary artery. A significant left-to-right shunt was noted with early cardiac decompensation as evidenced by the slight elevation of the left ventricular end-diastolic pressure and left ventricular hypertrophy despite the patient's being asymptomatic. Ligation of the anomalous left coronary artery was performed to improve his myocardial perfusion and because of the frequency of sudden death in these patients.[1,7,8] That this objective was accomplished is assumed by the demonstrable reduction in heart size in subsequent follow-up. The distinct possibility does exist that some myocardial function may be compromised since the apical systolic murmur that persists may infer dilatation of the mitral ring.

Definitive surgical treatment of this anomaly by use of a Dacron graft and autologous vein graft with anastomosis of the left coronary artery to the aorta has been reported by Cooley and co-workers[9] in a 4- and 5-year-old with excellent results. This approach now seems technically feasible and would appear to be the more desirable approach in situations where it appears technically possible. The long-term prognosis as regards coronary artery disease would no doubt be better in a "two-coronary heart" as opposed to a "one-coronary heart."

Our patient must be considered as additional evidence that patients with this anomaly may become asymptomatic adults with marginal collateral circulation. It should be noted that in some older patients a machinery murmur is not noted.[1,4] This infers hemodynamically insufficient collateral flow to reflect an audible continuous murmur.[7] This valuable physical sign is emphasized as an additional tool to determine the degree of collateral coronary flow to the myocardium. Hence its prognostic value is evident when surgical intervention is contemplated. A murmur of ominous significance is that of mitral regurgitation.[3,11] The development of significant mitral regurgitation in these patients may indicate diffuse left ventricular myocardial fibrosis secondary to an inadequately developed collateral circulation which offers a poorer surgical candidate.

Summary

A case report of surgical ligation of an anomalous left coronary artery in an adult has been presented. This rarity in the adult has been compared to the other few reports noted in the literature and valuable prognostic signs are emphasized on the physical

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examination. With the limited case reports in the older individual it appears that good retrograde flow from the right coronary artery through the collaterals and left coronary artery into the pulmonary artery is of extreme importance prior to consideration for surgical intervention. Additional long term follow up evaluation of older patients with this malformation is needed for definitive evaluation of the therapeutic procedures undertaken. The recent advances in the technique of coronary angiography promise to be an aid in solving this problem.

REFERENCES

1. Lampe C. G and Verhengt, A P Anomalous left coronary artery Adult type, Am Heart J 59 769 1960.
2. Talner N S., Halloran, K. H Mahdavy M Gardner T H and Hipona, F Anomalous origin of the left coronary artery from the pulmonary artery A clinical spectrum, Am. J Cardiol 15:689 1965.
3. Massih, N A Lanier J and Vermillion, M Myocardial ischemia after ligation of an anomalous left coronary artery arising from the pulmonary artery New England J Med. 269:483, 1963.
4. Likar I Criley J M., and Lewis, K. B Anomalous left coronary artery arising from the pulmonary artery in an adult A review of the therapeutic problem, Circulation 33 727 1966.
5. Roche, A H G.: Anomalous origin of the left coronary artery from the pulmonary artery in the adult, Am. J Cardiol. 20:561 1967
6. Gouley B. A Anomalous left coronary artery arising from the pulmonary artery (adult type) Am. Heart J 40:630, 1950
7. Agustsson M H Gasul, B. M Fell E. H. Graettinger J S Bicoff J P and Waterman, D F Anomalous origin of the left coronary artery from the pulmonary artery Diagnosis and treatment of infantile and adult types, J.A.M.A. 180:93 1962
8. Liebman, J C Hellerstein, H K Ankeney J C and Tucker A The problem of anomalous left coronary artery arising from the pulmonary artery in older children Report of three cases, New England J Med 269 486 1963.
9. George, J M and Knowlan, D M Anomalous origin of the left coronary artery from the pulmonary artery in an adult, New England J Med 261:993, 1959
10. Cooley D A. Hallman G L., and Bloodwell, R. D Definitive surgical treatment of anomalous origin of left coronary artery from pulmonary artery Indications and results, J Thoracic & Cardiovas Surg 52 798, 1966.
11. Leman, A., Fernandez, B., Uricchio, J F and Nichols H T Aberrant origin of the left coronary artery combined with mitral regurgitation in an adult, Am J Cardiol. 8 130, 1961
12. Burchell, H B, and Brown, A. L J Anomalous origin of the left coronary artery from pulmonary artery masquerading as mitral insufficiency Am. Heart J 63:388, 1962

Decrease in pulmonary vascular resistance following surgical closure of a ventricular septal defect associated with elevated capillary wedge pressure and severe pulmonary arterial hypertension

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The results of surgical closure of ventricular septal defect with increased pulmonary vascular resistance have been discouraging, for the pulmonary vascular resistance has not decreased after operation. These poor results, however, only emphasize the need to discover those patients, however uncommon, in whom surgical treatment results in a decrease in pulmonary vascular resistance.

Increased pulmonary vascular resistance secondary to left ventricular failure and pulmonary venous hypertension is rarely encountered in uncomplicated ventricular septal defect. This form of pulmonary hypertension is reversible, however, and it is important to recognize those patients in whom surgical treatment would reduce the pulmonary vascular resistance. The purpose of this report is to document the reversibility of this type of pulmonary hypertension in a patient with ventricular septal defect.

Case report

A 2 year-old girl was evaluated because of growth failure, unusual sweating, and dyspnea with exertion. Treatment with digitalis produced no significant change in her clinical course. She was an undernourished child. There was no visible cyanosis. There was prominent intercostal space retraction with inspiration. The heart was dilated to the anterior axillary line, and the right ventricle was hyperdynamic. The second heart sound was single. A Grade 3/6 pansystolic murmur was heard along the lower left sternal border. No diastolic murmurs or abnormal sounds were present. The liver was enlarged and felt 3 cm. below the right costal margin.

Right ventricular hypertrophy was evident on the electrocardiogram (ECG).

The left atrium displaced the barium-filled esophagus posteriorly, and the pulmonary vascular shadows were prominent, as seen in the chest x-ray.

The data obtained by cardiac catheterization, with the patient sedated, are tabulated in Table I and show a small left-to-right shunt into the right ventricle, severe pulmonary hypertension, and an elevated pulmonary capillary wedge pressure.

Although the risk of surgical treatment was thought to be great, it was decided to close the ventricular defect.

After operation the patient's exercise tolerance improved, her body weight increased, and she was generally improved. No murmur was detected after the operation, and the second heart sound split normally.

A second cardiac catheterization was done when the patient was 3½ years of age, approximately 1½ years following closure of the defect. The data are presented in Tables I and II. The pulmonary arterial blood pressure and the capillary wedge pressure

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Table I

Patient data	Before operation				1½ years after operation			
	PACw	*PA*	*FA*	*RA*	*PACw*	*PA*	*FA*	*RA*
Mean pressure (mm. Hg)	20	70	75	10	8	18	65	3
Saturation (per cent O_2)	95	77	95	74	97	78	97	78
Flow ratio	—	1.16	—	—	—	1.00	—	—
Pressure ratio	—	0.76	—	—	—	0.16	—	—
Resistance ratio	—	0.65	—	—	—	0.16	—	—
RV pressure (mm. Hg)	100/0/20				30/0/6			
Body weight (lb.)	20¾				32½			
Age (yr.)	2				3½			

Abbreviations: PACw, pulmonary capillary wedge; PA, pulmonary artery; FA, femoral artery; and RA, right atrium.

Table II

$$\frac{\text{Pulmonary}}{\text{Systemic}}\ \text{Flow ratio} = \frac{\text{Pulmonary flow}}{\text{Systemic flow}} = \frac{\dfrac{O_2\ \text{consumption}}{LA\ O_2 - PA\ O_2}}{\dfrac{O_2\ \text{consumption}}{\text{Aorta}\ O_2 - RA\ O_2}} = \frac{\text{Aorta}\ O_2 - RA\ O_2}{LA\ O_2 - PA\ O_2}$$

Oxygen saturation was substituted for O_2 content

$$\frac{\text{Pulmonary}}{\text{Systemic}}\ \text{Pressure ratio} = \frac{\text{Mean PAp} - \text{Mean LAp}}{\text{Mean FAp} - \text{Mean RAp}}$$

The resistance ratio can be defined as the value obtained by the relationship

Pressure = flow × resistance

$$\text{Resistance ratio} = \frac{\text{Pressure ratio}}{\text{Flow ratio}}$$

Abbreviations: LA, left atrium; O_2, oxygen; p, pressure.

ere normal. The right ventricular end-diastolic pressure, which had previously been elevated and corresponded to the capillary wedge pressure, was normal. There was no evidence of intracardiac shunt.

Discussion

The need to identify patients with reversible pulmonary hypertension associated with congenital heart disease has been expressed in recent literature. It is generally accepted that patients with an elevated pulmonary vascular resistance are poor candidates for surgical correction, not only because the immediate surgical mortality rate is greater but also because the pulmonary arterial pressure is not likely to decrease.[3-4] For this reason it is important to recognize the patient with reactive pulmonary hypertension which is reversible.

Patients with ventricular septal defect and congestive heart failure most frequently have a low or normal pulmonary vascular resistance. In fact it is believed that the low pulmonary vascular resistance permits the large pulmonary blood flow which overloads the ventricular myocardium and results in myocardial failure

In contrast to this patients with myocardial failure but without ventricular septal defect often have increased pulmonary vascular resistance and pulmonary hypertension as a result of elevated pulmonary venous pressure. Since the degree of pulmonary venous hypertension may be equal in the two groups it is surprising that more patients with ventricular septal defect and left ventricular failure do not have increased pulmonary vascular resistance.

In patients with ventricular septal defect large volume shunt and left ventricular failure it might be postulated that an increase in pulmonary venous pressure would result in increased pulmonary vascular resistance and a reduction of the volume flow. This in turn might reduce the end-diastolic pressure. The stimulus to reflective increase in pulmonary vascular resistance would thus be removed and the volume flow could again increase. A dynamic equilibrium would thus be established with the left-to-right shunt regulated by the effect of pulmonary vascular resistance on ventricular volume load and the pulmonary vascular resistance in turn partly regulated by the left ventricular end-diastolic pressure.

The stimulus of pulmonary venous hypertension is capable of increasing the pulmonary vascular resistance whether found in association with isolated mitral obstructive disease or with ventricular septal defect as in this patient. Further the pulmonary vascular resistance may return to normal when the cause of the pulmonary venous hypertension is eliminated.[4]

This combination of hemodynamic changes with ventricular septal defect is quite rare. This was the only case found among 200 patients with ventricular septal defect whose data were reviewed.

Since the recognition of this form of reversible pulmonary hypertension depends on the demonstration of pulmonary venous hypertension the importance of adequate measurement of the reflected left atrial pressure should be emphasized. In patients with uncomplicated ventricular septal defect the elevated capillary wedge pressure is a reflection of an elevated left ventricular end-diastolic pressure. In those ventricular defects large enough to allow equilibration of pressure through the defect, the left and right ventricular end diastolic the left atrial and the pulmonary capillary wedge pressures will be equal.

The fact that pulmonary arterial hypertension and increased pulmonary vascular resistance can occur as a consequence of pulmonary venous hypertension in patients with ventricular septal defect is illustrated by this patient. Since the right ventricular end-diastolic and the pulmonary capillary wedge pressures were equal ventricular myocardial failure appears to be responsible for the elevated pulmonary venous pressure. More important the pulmonary vascular resistance returned to normal following surgical closure of the ventricular septal defect. When this combination of findings is encountered in the patient with isolated ventricular septal defect a pessimistic prognosis seems unwarranted.

Summary

A patient with isolated ventricular septal defect and increased pulmonary vascular resistance associated with elevated pulmonary capillary wedge pressure is presented. The pulmonary vascular resistance returned to normal following closure of the ventricular defect.

Patients with increased pulmonary vascular resistance complicating isolated ventricular septal defect rarely have elevation of the pulmonary capillary wedge pressure. Although this combination of circumstances is rarely encountered its recognition is important because of the potential reversibility of the pulmonary hypertension following surgical treatment.

REFERENCES

1. Leachman, R. D. and Gunn, G. Observations on the second heart sound following surgical closure of ventricular septal defects, Cardiovas. Res. Center Bull. 1:56, 1962.
2. Reeves, R. Selzer, A., Popper, R. W. Leeds, R. F. and Gerbode, F. Reversibility of pulmonary hypertension following cardiac surgery, Circulation 38:1, 1966.
3. Leachman, R. D. Observations on the pulmonary vascular resistance following surgical closure of high resistance ventricular septal defects, Cardiovas. Res. Center Bull. 2:21, 1963.
4. Braunwald, N. S. Braunwald, E., and Morrow

A. G.: Effects of surgical abolition of left to right shunts on the pulmonary vascular dynamics of patients with pulmonary hypertension, Circulation 26 1270, 1962.

5. Lucas, R. V J Adams, P Jr Anderson, R. C Meyne, N G., Lillehei, C. W and Varco, R. L. Natural history of isolated ventricular septal defect: A serial physiologic study Circulation 24 1372, 1961

6. Hallman, G L., Cooley D A. Wolfe, R. R. and McNamara, D G. Surgical treatment of ventricular septal defect associated with pulmonary hypertension J Thoracic & Cardiovas. Surg 48:588, 1964.

7. Dexter L. Pathologic physiology of mitral stenosis and its surgical implications, Bull. New York Acad. Med. 28:90, 1952

Clinical pathologic conference

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History

A Caucasian man 41 years of age was first admitted to the Research and Educational Hospitals on March 23, 1966. The patient's symptoms began in December when he developed a cold, with cough without production of sputum. One month later he began to notice progressive shortness of breath and ankle edema. Later the edema extended up to the inguinal area accompanied by progressive orthopnea and paroxysmal nocturnal dyspnea. The patient denied alcoholic intake, drug addiction, or exposure to toxic substances. On admission, the patient had a blood pressure of 105/80 mm. Hg, pulse 108 per minute, respirations 22. There was no distention of the neck veins or enlargement of the thyroid. There were a few moist râles at the bases of the lungs posteriorly. No friction rubs were heard. The left border of cardiac dullness could not be percussed, but the heart was thought to be enlarged. There was a normal sinus rhythm. An S_3 and S_4 could be heard. There were no heart murmurs. The liver edge was 2 cm. below the right costal margin. No other organs were palpable. Urinalysis showed a specific gravity of 1.015 and subsequently was measured as 1.020. There was no albuminuria or glycosuria. No cells were seen on high-power microscopic examination. The hematocrit on admission was 46 per cent, and white blood count (WBC) was 10,100 with a normal differential. Adequate platelets were seen on differential smear. The Venereal Disease Research Laboratory test (VDRL) was negative. Serum chloride was 101 mEq. per liter, carbon dioxide combining power 26 mEq. per liter, serum sodium 141 mEq. per liter, serum potassium 4.3 mEq. per liter. The blood urea nitrogen (BUN) was 25 mg. per cent. The following values for serum were obtained: cholesterol 301 mg. per cent, total serum lipids 7.0 mg. per cent, protein-bound iodine (PBI) 5.2 mcg. per cent, serum glutamic oxaloacetic transaminase (SGOT) 11 units, total bilirubin 1.05 mg. per cent, and serum lactic dehydrogenase (LDH) 350 units. Urine and multiple blood cultures were negative. X-ray of the chest revealed a markedly enlarged heart with prominence of the left ventricle and suggestion of mild left atrial enlargement (Fig. 1). The electrocardiogram (ECG) on admission had a normal sinus rhythm with evidence of left ventricular and left atrial hypertrophy (Fig. 2). Near the time of discharge and after therapy with digitoxin, the patient was found to have sinus rhythm with multiple premature ventricular contractions. T waves were inverted in V_5 and V_6. There was evidence for left atrial hypertrophy and left ventricular hypertrophy. The initial findings on cardiac catheterization yielded evidence for left and right ventricular failure with elevated left and right end-diastolic pressures and low cardiac output with little increase on exercise. Coronary arteriograms showed patency of these vessels with a dominant right and small left coronary artery. The patient was treated with digitoxin and prednisone. The dosage of prednisone was 30 mg. by mouth twice a day. After two weeks of therapy the cardiac output had risen slightly. However, it was still low and with subnormal rise in output after exercise. Pulmonary pressure was normal at rest, and the right ventricular diastolic, systolic, and right atrial pressures were normal at rest and with exercise. Steroids were discontinued April 26, 1966, since there was marked improvement in the patient's cardiac condition. The ECG now showed voltage criteria for left atrial hypertrophy but QRS voltage had decreased and no longer met criteria for left ventricular hypertrophy. ST-T changes were consistent with digitalis effect or questionably ischemia. After discharge, the patient washed cars all summer and on Sept. 6, 1966, it was decided to discontinue his digitoxin and other medications. Shortly thereafter he noted a return of his symptoms. He had dyspnea on exercise, orthopnea, and paroxysmal nocturnal dyspnea. In October, 1966, he was again placed on digitoxin and prednisone. He noted that his symptoms persisted and seemed to be increasing in intensity. He was admitted for the second time on Dec. 6, 1966.

Physical examination. The patient was well developed and well nourished and in moderate respiratory distress. Blood pressure was 110/90, respirations 24, pulse 110, and regular. Eyes: sclerae

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Fig. 1 X-ray of the chest with enlargement of the heart, predominantly left ventricular.

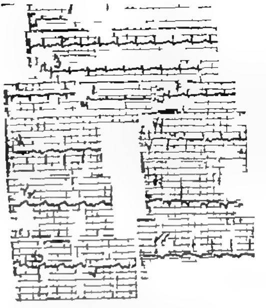

Fig. 2 ECG March 23, 1966. Rate 104 rhythm sinus with premature ventricular contractions. PR duration 0.16 sec. QRS duration 0.08 sec., QRS vector (frontal plane) +30° T vector (frontal plane) −120° P waves are broad and biphasic in V1. The ST segments are depressed in II, AVF, V_{4-6}, and elevated in V to V. The T waves are inverted in V_{4-6}.

clear; fundi within normal limits. Neck: supple, without adenopathy, but neck veins were distended at 45 degrees. Chest: slightly increased in anteroposterior (AP) diameter. Lungs: resonant with few inspiratory râles at both bases. Heart: point of maximal impulse was not palpable. The left border of cardiac dullness was 3 cm. to the left of the midclavicular line; regular rhythm; S_1 and S_2 sounds were normal but soft S_3 was present at the left sternal border. No murmurs were heard. Abdomen: liver edge was felt 2 cm. below the right costal margin; no other organs or masses were palpated. Extremities: 3 plus pitting edema of both ankles and pretibially.

Laboratory data. Urinalysis: clear, yellow urine with specific gravity 1.015, pH 5, albumin trace, no sugar or cells. WBC was 15,350 with normal differential. Hematocrit was 52, hemoglobin 16.4. Platelets were normal. Sodium was 131 mEq. per liter on Dec. 6 and fell to 121 on Dec. 30. During this same period, potassium rose progressively from 4.6 to 7.1 mEq. per liter; chlorides fell from 97 to 86 mEq. per liter; carbon dioxide combining power fell from 26 to 16 mEq. per liter; BUN rose from 28 to 68 mg. per cent, creatinine rose from 1.7 to 3.1 mg. per cent, and SGOT rose from 96 to 580 units. On Dec. 30 the serum amylase was 452 units; serum LDH was 670 on Dec. 6 and 940 on Dec. 12. The fractionated LDH on Dec. 19 was labile 125, stable 960 for a total of 1,085. Serum electrophoresis on Dec. 7 yielded G 17.6, β_2 5.6, β 10.6, A 13.4, A 7.7 and albumin 45.1 for a total protein of 4.7 Gm. per cent. Repeated blood cultures were negative. Cerebrospinal fluid was normal. Chest x-ray showed generalized, marked cardiomegaly. Portable chest x-ray on Jan. 1, 1967 showed vague infiltrate in the right lung field. ECG's dated Dec. 7, 1966 showed rate 95, PR duration 0.19 sec., QRS duration 0.08 sec., approximate QRS frontal vector +30 degrees, and mean T vector of −15 degrees. Premature ventricular contractions and auricular contractions appeared since the last ECG taken Nov. 12, 1966. T-waves were inverted in I, II, AVF, and isoelectric in III with ST-T depression in V and V_6. ECG dated Dec. 20 showed rate 163 with nodal tachycardia. T-wave inversion in V with ST elevation in V. ECG dated Dec. 29 showed rate 102 with sinus tachycardia and first degree A-V block. QRS vector was now −30 degrees. The diffuse intraventricular conduction defect present earlier the same day had disappeared, but the ECG continued to show poor R wave progression in V_{1-4} and ST-T wave changes in V_{4-6} (Fig. 3).

Hospital course. The patient continued to have marked symptoms of congestive heart failure and was vigorously treated with digitoxin and diuretics with only slight improvement. He was barely able to walk around and at most times stayed in bed. He was given the anticoagulant heparin, 75 mg. intravenously every four hours. Approximately two weeks before he died, he was started on 30 mg. prednisone twice a day. On Dec. 27, 1966 he was noted to have a potassium of 6.7 and the hyperkalemia was felt to be secondary to the diuretics. For this reason both the Hydrodiuril and the Aldactone were stopped. On Dec. 29 he was noted to

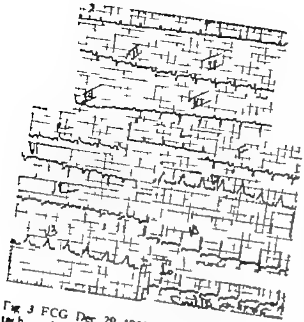

Fig. 3 ECG Dec 29 1966 Rate 102 rhythm sinus tachycardia with first-degree AV block. PR duration 0 20 sec. QRS duration 0 08 sec. QRS vector (frontal plane) −30° T vector (frontal plane) indeterminate The QRS axis has shifted to the left There is voltage evidence of left ventricular hypertrophy The T waves are inverted in V and flat in the frontal lead suggesting ischemia. Large broad negative P waves in V are consistent with left atrial hypertrophy

ha marked left axis shift on his ECG and his QRS complexes had widened suspiciously By Dec 29 his potassium was up to 6 7 compared to 5 9 the day before Blood gases were not remarkable. He was treated with insulin and glucose, but on Dec 30 he was noted to have a potassium of 7 1 He was hyperventilating his pCO₂ was down to 12 mm Hg with 100 per cent oxygen saturation and a pO_2 of 160 mm Hg with oxygen flowing. The patient was given several ampules of calcium chloride and calcium gluconate 40 mg of furosemide intravenously and 4 mg of morphine, with marked improvement The QRS narrowed to almost half and it was felt that, by stopping the Aldactone and Diuril abruptly his potassium was driven up because of the longer duration of action of the Aldactone The patient was followed closely on the cardiac monitor and with little change in the electrographic criteria he gradually became more comatose and died on Jan. 2 1967

Discussion

DR. GUNNAR This is the history of a patient who was first admitted to the Research and Educational Hospitals in March 1966 with a 3 to 4 month history of a cold This "cold" was described as a cough which was nonproductive The illness was not described as associated with fever or evidence of an upper respiratory infection and I must assume that the cough as described is more representative of early congestive heart failure than infection. It would be helpful to know whether the cough was worse at night and was relieved by sitting up but this information is apparently not available One month later he began to notice increasing dyspnea and edema with the edema gradually extending up to the inguinal area. We can conclude that the patient had rather rapidly progressed from good health to severe congestive heart failure over a period of 3 to 4 months. He gave no history of chest pain and no history of trauma to the legs. He denied alcoholic intake or drug addiction.

Physical examination on his first admission revealed a blood pressure of 105/80 which is a small pulse pressure consistent with any form of myocardial disease. His pulse was slightly rapid and neck vein distention is not described This is a disturbing feature, for if this patient had cardiac failure, as is indicated by all other signs, then he should have had distention of the neck veins. If he had this much edema without neck vein distention one would be inclined to consider a nephrotic syndrome, which would be difficult to substantiate without albuminuria or liver disease, which is not substantiated later on If I must disregard something in this protocol I will choose to disregard this particular notation realizing that the last time I took this course for this same exercise about a year ago I missed an important clue for the diagnosis of sarcoid of the heart. The lungs showed some evidence of congestion and the heart which was enlarged had sinus rhythm There were no murmurs, but a fourth heart sound and a third heart sound were described The fourth heart sound represents the presystolic atrial gallop sound which is a sign of loss of compliance of the ventricle from which the sound arises. The third heart sound is the protodiastolic gallop sound which signifies rapid ventricular filling and indicates that the patient had some diastolic overload of the ventricle from which the sound arises. We then have evidence of systolic and diastolic overload of the ventricles and

this would be consistent with a diagnosis of some form of myocardial disease which has decreased the compliance of the ventricle as well as dilated the ventricle. Although there are no murmurs, we would consider this patient in group III of myocardial disease, the type of heart disease which resembles arteriosclerotic heart disease. The remainder of the physical examination is consistent with cardiac failure. The liver edge was down 2 cm. and urinary findings were negative except for a very high specific gravity. The blood count, serum electrolytes, PBI and SGOT were all normal. The BUN was minimally elevated, the total cholesterol was elevated at 301 mg. per cent, and the total serum lipids were slightly elevated to 770 mg. per cent. The total bilirubin was 1.05 mg. per cent which is not inconsistent with cardiac failure. All of the blood cultures and urine cultures were negative. X-rays of the chest revealed an enlarged heart with prominence of the left ventricle. The ECG on admission confirmed the presence of normal sinus rhythm, and there was evidence of both left ventricular and left atrial hypertrophy. The patient was treated in the usual manner for cardiac failure, and in the course of digitalization developed some premature ventricular contractions as well as inversion of his T waves in Leads III, IV, and V. The arrhythmia could be due to digitalis excess or may be a reflection of his myocardial disease. Cardiac catheterization showed an elevation of the end-diastolic pressure in both right and left ventricles, indicating biventricular failure which was also manifested by low cardiac output and very little rise in cardiac output on exercise. Coronary arteriograms showed normal coronary arteries. In addition to treatment with digitoxin, the patient was placed on prednisone, 60 mg. per day. After two weeks there was a return of the end-diastolic pressure in the right ventricle to normal levels. The steroid therapy was discontinued after a very short course, because the patient had shown marked improvement. There was some loss of left ventricular voltage during this period, and this would indicate either a decrease in the workload of the left ventricle or, more likely, an increase in fibrosis with replacement of myocardium by electrically inert tissue. One should also think of pericardial fluid, but this should have been recognized on the right heart catheterization. The patient apparently made a remarkable recovery and returned to work as a car washer. He did so well that it was decided to discontinue his digitoxin and other medications. Shortly after this, the patient had a return of his symptoms and, despite the reinstitution of digitalis and steroid therapy, he was readmitted in failure in December, 1966. At this time physical examination revealed a well-nourished man in moderate respiratory distress. His blood pressure was 110/90, the slight elevation in the diastolic pressure being consistent with cardiac failure. It is now noted that the neck veins were distended, but the waves in the neck are not described. The lungs again showed evidence of congestion, the heart was evidently quiet since the point of maximum impulse was not palpable. However, the heart was distinctly enlarged, and the fourth heart sound is no longer described, although a third heart sound was still present, and no murmurs were heard. The liver was down 2 cm., and there was pitting edema of both ankles. The urinalyses at this time again was unrevealing. There was only a trace of albumin, which is minimal even for the extent of failure. His hemoglobin was slightly elevated, and this, I think, would be consistent with stress polycythemia of failure. The tests during this hospital course showed a low sodium, which would be consistent with dilutional hyponatremia. The chloride was similarly slightly low. The potassium level rose during this hospitalization as did the urea nitrogen. The cholesterol was now very low at 127 mg. per cent, and both the SGOT and LDH revealed a very high stable level, which I cannot brush off as a sign of pulmonary embolus or severe cardiac failure; rather, this leads me back towards the diagnosis of some abrupt type of myocardial degeneration. Serum electrophoresis showed a somewhat depressed total protein, a low albumin level, and a remarkably high α-2 globulin level. This level would suggest that we are dealing with some form of subacute infection and would be the only other sign in this patient

besides the edema that we might be dealing with a nephrotic syndrome—or this could be a manifestation of myocardial infarction Again repeated blood cultures were negative and the chest x rays showed progressive cardiomegaly Near the end of the illness a portable chest x ray showed a vague infiltrate of the right lung field which could be a pulmonary embolus and this would be very common as a terminal event in a patient with chronic cardiac failure. The ECG now revealed premature ventricular and atrial contractions and in addition progressive T wave inversions over the left ventricle. On Dec. 20 the patient developed a nodal tachycardia with a rate of 163 and subsequent to this, the QRS axis moved to −30 degrees, suggesting damage to the free wall of the left ventricle. A diffuse intraventricular conduction defect is later described and this is consistent with the high potassium levels and indeed is corrected as the potassium is brought down. During his hospital course the patient was so dyspneic he was in bed most of the time. He was anticoagulated with heparin and again placed on prednisone He developed a hyperkalemia which is explained by the use of Aldactone The patient hyperventilated which accounts for some of his pCO_2 changes. Despite correction of the hyperkalemia with the use of furosemide the patient became more comatose and died on Jan 2 1967

This entire report is one of severe and progressive myocardial degeneration with cardiac failure The most common etiology would be coronary artery disease. The only inhibition in my making this diagnosis is the normal coronary arteriograms done during the first admission. Review of the arteriograms shows a normal and dominant right coronary artery The left coronary artery is smaller and no definite area of occlusion can be visualized although a good circumflex branch is never seen. I would agree that the evidence against occlusion of a major coronary artery is convincing enough to make me eliminate this as the cause of this patient s myocardial disease.

We now are left with nonvascular causes of myocardial degeneration unless there is disease of the small coronary vessels. This would be difficult to classify in our present state of knowledge, since this has been a poorly described entity prior to the studies of James. Most of the patients with diffuse small vessel disease of the myocardium are classified elsewhere, since this is associated with collagen and hypersensitivity disease such as hypersensitivity angiitis.

The primary myocardial diseases are a large group of diverse etiology in which the myocardial disease is the primary cardiac defect and this is unassociated with coronary valvular or shunt flow changes. In the department of Adult Cardiology at Cook County Hospital we have studied 267 such patients in the past three years. It must be kept in mind that these patients were entered in the series because they presented with myocardial failure not explained by coronary hypertensive or valvular disease. The number with arteriosclerotic heart disease was kept at a minimum because we limited the group to patients below the age of 45 The largest number in our group were patients who had myocardial disease associated with alcohol and this included 118 of the 267 patients. The patient we are discussing today denies alcoholic intake. However one should note that he is a car washer and these individuals frequently need something to warm them up in the cold weather so although I do not wish to challenge the veracity of the patient I would suggest that there may have been some slight inaccuracy in his description of the type of beverage he preferred If we look at the rest of the group of patients we have studied there were 34 associated with viral infections, particularly the Coxsackie group and in two patients we have been able to isolate this virus by myocardial biopsy Six of our patients have had myocardial disease associated with psittacosis. Neither of these infections was established in the patient under discussion today and the viral etiology is not suggested by either the presence of pericarditis at the onset of his illness or a well-defined upper respiratory illness preceding his cardiac failure The patient, according to the protocol was not noted to have been in contact with parakeets. Five of our patients were found to have some collagen disease which certainly

would be possible in the patient we are discussing today particularly with the evidence of progressive renal failure. However it would have been more consistent had there been definite evidence of renal disease in the urinalysis. I am certain that a normal urinalysis does not preclude the diagnosis of lupus erythematosus, but it certainly makes it less likely in a patient with progressive renal disease. The rest of the patients we have studied have had other diseases 16 eventually were proved to have tuberculous pericarditis, six were associated with various bacterial infections, and 19 occurred in the postpartum period which I think is eliminated in this patient. The rest had a scattering of neuromuscular disorders sarcoid thyrotoxicosis, hypertensive cardiovascular disease, giant cell myocarditis, and unclassified myocardial disease. Six of our patients eventually turned out to have myocardial infarction or were proved to have had severe coronary artery disease which emphasizes the fact that patients presenting as a primary myocardial disease may actually have severe coronary artery disease. In summary then I would choose as my diagnosis primary myocardial disease due to a viral myocarditis with the question of alcoholism as the etiology or aggravating factor still unanswered We have one remaining difficulty and that is the reason for the renal failure and this could be just due to severe progressive myocardial failure or could be embolic in nature or represent some underlying renal disease existing prior to his present illness. Periarteritis should of course be mentioned but in the absence of abdominal pain neurologic manifestations, or eosinophilia I think its introduction at this point would be purely CPC manship.

DR. KRAKOWER There was no peripheral edema at the time of autopsy Pleural and peritoneal cavities were free of fluid The pericardial sac contained 5 to 10 c.c. of straw-colored liquid The heart was enlarged It weighed 760 grams (normal 350 to 450) The parietal and visceral pericardial surfaces were not remarkable The right atrium was enlarged measuring in the fixed state 7.5 cm. in circumference and 7.5 cm from superior to inferior vena cava. It was also hypertrophied as indicated by a myocardial thickness of 0 2 cm. and by thickened widened pectinate muscles. The endocardium was not remarkable. The fossa was imperforate. The tricuspid ring measured 13 5 cm. in circumference (normal 12) The cusps of the tricuspid valve showed some hemodynamic thickening The chordae tendineae were likewise thickened as were the two major papillary muscles. The right ventricle was enlarged The inflow tract measured 10 cm in length and the outflow 13 0 cm There was also appreciable hypertrophy with the myocardium in the proximal part of the inflow tract measuring 0.5 cm. in thickness (normal 0.02 to 0 03) that of the middle portion of the outflow tract measuring 0 6 cm and that near the pulmonary valve, 0 45 cm. The trabeculae carneae were thick. Extending from the apex of the right ventricle and attached to the posterior and lateral walls there was an antemortem thrombus measuring 6 cm. in length and 2.0 cm in maximal transverse diameter The parietal band was 2 5 cm wide and distinctly hypertrophied The septal band was broad and flat. The conus was smooth. The pulmonic ring measured 7 0 cm. in circumference (normal 8.5) The leaflets of the pulmonary valve were somewhat thicker than normal. The pulmonary artery immediately above the valve measured 6.5 cm. in circumference. Its wall measured less than 0 1 cm in thickness. There were no atheromatous plaques in the main pulmonary artery or its immediate branches. The left atrium was enlarged with a circumference of 12.5 cm. and a depth of 8 5 cm. from pulmonary vein to the ring of the mitral valve. It was also hypertrophied with a maximal myocardial thickness of 0.4 cm (normal 0 1 to 0 2) Its endocardium was not remarkable. The mitral ring measured 12.5 cm. (normal 10) The cusps of the mitral valve were not thickened The chordae tendineae were not thickened The left ventricle was appreciably enlarged. Its inflow tract measured 10.5 cm in length and its outflow 10 2 cm. It was also hypertrophied The myocardium measured 1.3 cm in thickness near the base of the inflow tract, 1 0 cm in the midregion of the outflow tract, and 1.5 cm near the aortic valve (normal 0.8 to

Fig 4 Inflow tract of left ventricle a massive thrombus extends from beneath the posterior leaflet of the mitral valve to fill all of the dilated ventricle except the subaortic area of the outflow tract

Fig 5 Outflow tract of left ventricle the thrombus fills all of the ventricle except the subaortic area.

1 0) The astonishing finding was that virtually the whole left ventricle was filled with thrombus (Figs 4 and 5) Only the smooth subaortic area of the outflow tract was spared This area measured 3 cm in the long axis of the ventricle and 7 0 cm in the transverse axis. In part, the thrombus was quite firmly attached to the endocardium particularly between rather than over the trabeculae carneae The aortic ring measured 7 5 cm in circumference (normal 7 5) The cusps of the aortic valve were not remarkable. The aorta immediately above the valve measured 7 0 cm in circumference and 0 1 cm in thickness There were some atheromatous plaques in this region There was atheromatous thickening in the transverse aortic arch and intercostal streaking in the descending and thoracic aorta. The latter measured 4.5 cm in circumference. The coronary arteries arose normally The left descending coronary artery had an initial circumference of 1 0 cm It bifurcated 2 0 cm from its origin The right branch could be traced to the apex of the heart. It never exceeded 0.3 cm in circumference. The left branch was lost 8.0 cm beyond the bifurcation Its inner circumference likewise never exceeded 0.3 cm These vessels were patent and were essentially free of atherosclerosis. The left circumflex with an inner circumference of 0 7 cm narrowed rapidly and was lost after it gave off its obtuse branch It too was patent and free of atheroma. The right coronary artery had an initial inner circumference of 0 9 cm. It maintained this wide caliber until it gave off the posterior descending septal branch It could be followed beyond this division for 3 cm along the posterior sulcus. The posterior descending branch could be followed to the apex of the heart and in its proximal portion it maintained an inner circumference of 0 4 cm The right coronary and its branches were all patent and free of atheroma. The heart was sectioned transversely from apex to base. There was a good deal of mottling of the myocardium but otherwise there was little evidence of significant scarring or gross infarction Microscopically endocardial and myocardial lesions were more marked in the more apical portions of the interventricular septum and anterior and posterior walls

of the left ventricle There was evidence for longer-standing and more recent attempts at organization of the luminal thrombus of the ventricle This ranged from dense endocardial fibrosis to active advance of granulation tissue into the thrombus with progressive fibrosis in its deeper portions. This was associated in places with considerable lymphocytic and histiocytic infiltration. The Thebesian veins were likewise extensively involved. Many of them showed progressive mural thromboses associated with the organization of films of fibrinous thrombi. Others were occluded by recent thrombi while others again showed stages of organization of occlusive thrombi to the point where they were fully organized and canalized The myocardium proper revealed hypertrophy and in instances fatty metamorphosis of its muscular fibers with some interstitial edema and slight to more marked interfibral fibrosis. There were in addition old areas of scarring with loss of muscular fibers and more recent areas of myomalacia with a retained vascular pattern but with collapse and thickening of the fibrous framework. There were also terminal myocardial necrobiotic areas. Associated with many of these recent necrotic areas there were thrombi in the related arterioles. These thrombi appeared to be microemboli.

Gross thrombosis or thromboembolism was recognized in only two anatomical areas. There were a few emboli in the branches of the pulmonary artery and these were associated with an infarct in the right lower lobe of the lung measuring 6 by 2.5 cm. There was also a thrombus, possibly an embolus occluding the abdominal aorta from below the level of the renal arteries to the bifurcation of the aorta. There were no gross infarcts, recent or old of spleen or kidneys. However microscopically there were older and recent microemboli of small vascular branches in the spleen interlobular arteries of the kidneys, capillaries of the renal glomeruli and arterioles of the testis.

Aside from the embolic phenomena there was considerable chronic passive congestion of the lower lobes of the lungs with, however relatively little edema but with hemorrhages, older organized patches of pneumonia and areas of terminal bronchopneumonia. There was acute passive congestion of the liver with wide centrolobular necrobiosis. There were acute congestive changes in the other abdominal viscera.

Since the initial cause of this man's myocardial failure was not clarified by the necropsy I fully agree with the discussant that we are forced to ascribe it to a form of primary myocardial disease of unknown or uncertain etiology My object in presenting this case was not to tax the diagnostic ability of the discussant. It was rather to present one unusual complication and a number of questions.

In my own experience I have never seen a thrombus as in this case filling more than 75 per cent of the left ventricle. It is my suspicion based on the stages of repair in the heart that this massive thrombus was built up slowly over the three months dating from the time the patient returned with recurrent myocardial failure. It behooves us therefore in cardiac conditions with low ventricular output to consider the possibility that mural thrombi may reach proportions which in and of themselves are occlusive of the ventricle.

The progressive myocardial changes as indicated by the serum lactic dehydrogenase can be accounted for by (1) a wide and dominant right coronary artery but a narrow abnormally divided left, which may have been inadequate to have carried enough blood to the anteroseptal anterior and posterior walls of a dilated and hypertrophied left ventricle particularly in the face of a progressive decrease in left ventricular output (2) the coronary arterial microemboli originating from the thrombus in the left ventricle which led to a multiplicity of myocardial microinfarcts of different ages. However the question may be raised as to what role the extensive and progressive occlusive changes of the Thebesian veins may have played in inducing interstitial myocardial edema, loss of myocardial muscle fibers, and interstitial fibrosis.

With the degree of thrombosis of the left ventricle one might have expected massive embolism with gross infarcts in a number of organs. These were absent If we assume that the thrombus in the ab-

dominal aorta was autochthonous. There were, however very impressive showers of microemboli. Leaving aside the factors of cohesiveness or fragility of a ventricular thrombus, would a quiet heart as in this case with restricted diastolic filling and decreased compressive force of systole permit the release of microfragments from the surface of a thrombus but be unable to mount the shearing forces necessary to dislodge larger fragments from it? Finally would a different regimen in the use of anticoagulants have prevented the formation and/or accretion of the ventricular thrombus?

Diagnosis Primary myocardial disease of unknown etiology with occlusive thrombosis of the left ventricle.

REFERENCES

1 James, T N An etiologic concept concerning the obscure myocardiopathies, Progr Cardiovas. Dis. :43 1964.

Hemodynamic studies in patients with chronically implanted pacemakers

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The development and application of surgically implanted electronic pacemakers in patients with complete atrioventricular (A V) block has prevented sudden deaths and the morbidity associated with Adams-Stokes attacks in thousands of operated patients. It is only natural to expect that this dramatic change in the natural history of a once fatal disease would necessarily be associated with an improvement in cardiac function. It has long been known that the cardiac output in patients with chronic acquired complete heart block is abnormally low.[1-4] During temporary pacing with an electrode catheter placed in the right ventricle the cardiac output increases, sometimes to normal resting levels.[1-4] It is generally assumed that this improvement is maintained following implantation of a permanent pacemaker. This has not however been our experience. This report details our experience with 17 consecutive patients with complete heart block admitted to the medical wards of the Cincinnati General Hospital or the Cincinnati Veterans Administration Hospital who consented to have one or more cardiac output determinations performed.

Methods and procedures

Cardiac output was measured by an indicator-dilution technique. A thin-walled short teflon catheter was inserted into a brachial artery by the Seldinger technique for arterial blood sampling. A thin-walled radiopaque teflon catheter with a 2 c.c. capacity was passed under fluoroscopic control to the junction of the right atrium and superior vena cava. One milliliter of indocyanine dye (cardiogreen*) in a dose of 5.0 mg was injected slowly into the venous catheter and then rapidly flushed with 5 to 10 ml. of saline. The blood was withdrawn from the brachial artery at a constant rate of 38 ml. per minute, through a Gilford densitometer (Model 103†). The curves were recorded on a Texas Instrument‡ direct writing strip chart recorder at a paper speed of 5.08 mm per second. Reproducibility of duplicate dye curves was estimated by an on-line Lexington

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*Hynson, Westcott and Dunning, Inc., Baltimore, Md.
†Gilford Instruments Laboratory, Oberlin, Ohio.
‡Texas Instruments, Inc., Houston, Texas.

Table I

Patient	Age	Sex	Preoperative study										
			Supine rest						Exercise				
			Date of study	H.R.	C.O	C.I	S.V	R.A.P	H.R.	C.O	C.I	S.V	Inc. in C.O
G V	60	F	10/30/63	39	3 7	2 1	95	5 0	39	4 2	2 4	58	291
G B	40	M	6/17/64	30	3 7	1 8	123	2 1	30	4 6	2 3	153	185
P K.	53	M	None										
J B	71	M	1/ 2/64	35	6 1	3 2	174	3 8					
R Le.	69	F	9/14/65	34	2 9	1 7	85	1 3	34	4 3	2 5	126	422
C. M	74	M	3/ 4/64	30	2 4	1 3	80	2 4					
L S	65	M	3/13/64	36	3 2	1 7	89	0 9					
M E C	46	F	2/ 5/64	36	3 7	2 5	103	3 5	36	4 9	3 3	136	395
M C	29	M	10/13/64	42	7 5	3 8	179	1 1	58	9 8	4 9	169	276
R. L	72	F	None										
V E	57	M	None										
O C	76	M	8/26/65	35	4 3	2 4	123	3 3					
R. S	62	F	9/21/65	36	3 2	2 0	89	2 5	42	3 8	2 5	90	157
S B	75	M	9/24/65	31	1 5	1 0	48	8 0					
H H	74	M	10/22/65	36	3 0	1 8	83	0	36	3 7	2 2	103	377
R. B	61	M	None										
J F	75	M	None										

Abbreviations: H.R. Heart rate, beats per minute; C.O. cardiac output, L. per minute; C.I. cardiac index, L. per minute per square meter; ... increase in O_2 consumption
*Congenital heart block

Instrument analogue computer (Model 303.)*

At the end of the procedure the curves were calibrated with the same flow rate and sensitivity settings as were used during the study. A zero point and 2 calibration points were obtained. The cardiac output was calculated by the Stewart Hamilton formula.[4] Duplicate cardiac output determinations agreed within 10 per cent at rest and exercise and were averaged.

Heart rate during each dye-dilution curve was determined from a simultaneously recorded electrocardiogram (ECG). Expired air was collected in a Douglas bag for 3 minutes at rest and for 1 minute during exercise. Aliquot samples of expired air were analyzed for oxygen content according to the method of Scholander[5] and oxygen consumption was calculated. Supine resting right atrial and systemic arterial blood pressures were recorded on an Electronics for Medicine photographic recorder using Statham P23dB pressure transducers. Gauges were leveled 10 cm above the table top.

All resting cardiac output determinations were performed with the patient in the supine position. The patient exercised by walking on a level treadmill at speeds graduated between 1 and 3 m.p.h. to that effort which was maximally tolerated without undue discomfort or cardiac irregularities or until exhaustion. All exercise cardiac output determinations were performed after at least 5 minutes of exercise at a given work load. Resting cardiac outputs in patients with electrode catheters were always done at least 10 minutes after a rate change was induced.

The 17 adult patients averaged 62 years of age (Table I). The youngest patient, M. C., was only 29-years-old and had congenital heart block. The other subjects

*Lexington Instruments Corp., Waltham, Mass.

Post pacing study

Date of surgery	Date of study	Supine rest H.R.	C.O	C.I	S.V	R.A.P	Exercise H.R.	C.O	C.I	S.V	Inc. in C.O
10/11/63	1/28/64	72	4 2	2 4	58	3 1	72	5 4	3 1	75	284
6/23/64	3/18/66	72	3 5	1 7	50	1 1	72	7 2	3 5	101	381
3/ 6/63	7/26/63	66	3 2	1 7	48	2 2	66	4 0	2 1	61	385
None	None										
10/13/65	10/21/65	66	2 0	1 4	30	0	66	3 3	1 9	50	458
None	None										
None	None										
2/11/64	6/16/65	72	4 8	2 8	67	1 4	72	5 8	3 4	81	248
None	None										
10/11/64	10/23/64	72	3 3	2 0	44	3 3					
6/ 6/62	11/11/64	58	4 2	2 4	74	3 7	57	6 9	4 0	121	372
8/28/65	11/18/65	68	3 2	1 7	47	1 1	68	5 3	2 8	78	298
None	None										
9/27/65	None										
10/24/65	5/12/66	68	3 3	2 0	49	2 4	68	3 9	2 4	57	304
9/21/65	10/28/65	70	2 3	1 5	33	3 0	70	3 5	2 2	50	3 4
8/30/65	4/13/66	67	4 7	2 4	67	4 1	90	5 8	2 9	64	254

S.V stroke volume, milliliters R.A.P mean right atrial pressure mm. Hg; Inc. in C.O increase in cardiac output, milliliters per 100

had acquired complete heart block and their ages ranged between 40 and 76 There were 12 men and 5 women in the series.

The clinical evidence for coronary artery disease—that is angina pectoris a history of a previous myocardial infarction or characteristic electrocardiographic abnormalities prior to the development of complete heart block, was convincing in only 4 patients, P K. C. Mc. R. S. and R. H All subjects complained of tiredness or weakness to varying degrees. Six subjects admitted to dyspnea on exertion but only on direct questioning

Resting cardiac indices were determined in 1 subjects prior to surgery Six of these subjects were studied both before and after surgery Five additional patients were studied at rest postoperatively but not preoperatively Hence resting cardiac indices were determined in a total of 17 patients.

The response of the cardiac output to the stress of exercise was examined in 7 subjects preoperatively Five of these subjects were studied both before and after surgery Five additional patients were studied postoperatively but not preoperatively The average interval between surgical implantation of a permanent fixed-rate pacemaker and the postoperative study was 34 weeks (range 1 to 117 weeks) The site of electrode implantation was the left ventricle in 11 patients. In one patient R. Le the right ventricle was stimulated by means of a permanent transvenous electrode catheter and a fixed rate pacemaker

The hypothesis that chronic electrical pacing of the left ventricle could deplete the myocardium of catecholamines, which in turn might depress myocardial function was evaluated in animal experiments. Complete heart block was induced surgically in mongrel dogs weighing 19 to 22

*Medtronic, Inc., Minneapolis, Minn.

kilograms. The dogs were anesthetized with pentobarbital sodium (25 mg per kilogram) intubated and artificially respired Through a right thoracotomy and during a brief period of venous inflow occlusion the atrial septum was exposed through an atriotomy That area of the interatrial septum which contained the A-V node and bundle of His was permanently injured or lacerated by ligation of a single suture Left ventricular catecholamine concentrations were determined in the following groups of dogs.

Group 1 The first group was composed of 11 normal dogs. Nine dogs were put to death and ventricular samples were obtained In one dog a ventricular biopsy was taken first prior to production of complete heart block 2 weeks later the dog was put to death and a ventricular sample was taken Another dog was biopsied prior to production of complete heart block and again 2 weeks later prior to insertion of wire electrodes 2 weeks after continuous pacing this dog was put to death and a ventricular sample was obtained

Group 2 A second group was composed of a total of 10 dogs who had complete heart block of 2 weeks duration and included the 2 dogs in Group 1 described above In addition there were 8 dogs in whom previous control biopsies were not obtained Three dogs were put to death and ventricular samples were obtained Five other dogs were biopsied prior to insertion of wire electrodes and were subsequently paced continuously for 2 weeks they were then put to death and ventricular samples were taken Hence some dogs served as their own controls These dogs are indicated in Fig 4 as symbols which are connected by straight lines.

Group 3 Sham experiments were done in 2 dogs in whom a right atriotomy was performed with manipulation of the septum Ventricular samples were taken 2 weeks later at the time of death. In another dog the catecholamine concentration of a biopsy sample taken after 2 weeks of complete heart block was compared with tissue taken at the end of 4 weeks.

Group 4 In 4 additional normal dogs samples of the left ventricle were obtained 5 to 7 days after electrical stimulation of the left ventricle at a rate of 135 These dogs were caged in a quiet dimly lit room. On the basis of periodic monitoring of the ECG during the day it was estimated that the heart was paced at the pacemaker rate during most of each 24-hour period Myocardial tissue samples were taken from the free lateral wall of the left ventricle approximately ⅓ to ½ the distance cephalad from the apex Repeat samples were taken from adjacent but grossly normal tissue. Electrical pacing of the left ventricle in dogs with complete heart block was accomplished with wire electrodes implanted in and sutured to the left ventricle and connected to a fixed rate (75 impulses per minute) battery powered pacemaker which was implanted subcutaneously

All specimens were quick-frozen on dry ice. All tissue samples were analyzed for their catecholamine concentrations in the laboratory of Dr Thomas E. Gaffney by laboratory personnel who were unaware of the experimental design Tissue samples were homogenized with trichloracetic acid and the catecholamines in the extract were determined fluorometrically with minor modifications of the method of Crout and associates.[9] Concentrations of norepinephrine between 0.05 and 0.4 μg per gram added to a tissue homogenate which had no measurable intrinsic catecholamine fluorescence yielded an average recovery of 88 per cent.[10]

Results

In only one patient, S. [redacted] who was critically ill when studied and had the lowest resting cardiac index, was the right atrial pressure elevated above normal limits Following chronic pacing with a permanent pacemaker only one patient G. [redacted] the youngest subject with acquired heart block noted significant improvement in his strength and exercise tolerance. In none of the subjects followed postoperatively was there clinical evidence of new cardiac symptoms, progression of symptoms, or reason to suspect deterioration of the cardiac status.

Six patients were studied both before and after pacemaker implantation Although the cardiac index increased slightly in 3 individuals it fell in the other 3 (Table I Fig 1) The average cardiac index was 2.0 L. per minute per square meter of body

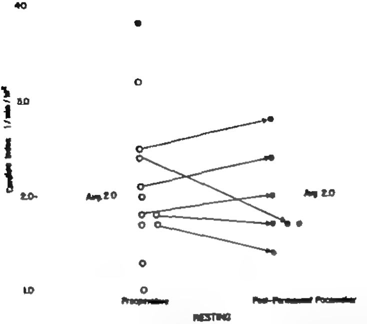

Fig. 1. The resting cardiac indices in 12 patients with complete heart block prior to implantation of permanent pacemaker are indicated by the open circles. One patient with congenital complete heart block is indicated by the symbol X and his value was not averaged with the others. The individual cardiac index values in 11 patients studied an average of 34 weeks following surgery are indicated by the closed circles. Straight lines connect 6 patients who were studied both before and after pacemaker implantation. The cardiac index increased slightly in 3 patients, and fell in the other 3. The average cardiac index was unchanged.

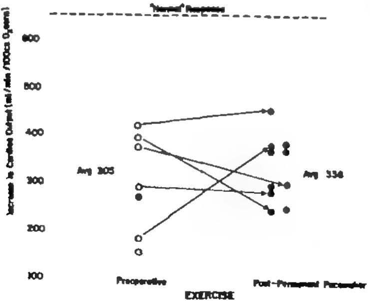

Fig. 2. The response of the cardiac output to treadmill exercise as measured in 7 patients preoperatively and in 10 patients an average of 34 weeks following implantation of a permanent pacemaker. The patient with congenital heart block X had an inadequate response to exercise. His value was not included in the average. The average preoperative response was approximately half normal and was but little improved postoperatively.

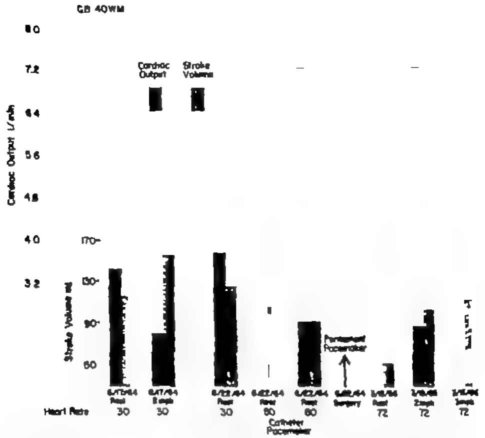

Fig 3 A longitudinal hemodynamic profile for patient G B is shown Cardiac output in L. per minute is represented by the solid bars The stroke volume in milliliters corresponding to that output is represented by the cross-hatched bar for each pair of values. The patient was studied twice preoperatively and once postoperatively Values for cardiac output and stroke volume at his idioventricular rate at rest and exercise, during temporary electrode catheter pacing at rates of 50 and 80 and at permanently paced rate at rest and exercise are demonstrated See text for details.

surface area preoperatively and was unchanged postoperatively In normal adults a cardiac index of about 2 6 might be expected at age 61 the average age of our patients. The subject with congenital heart block had a normal resting cardiac index.

The response of the cardiac output to treadmill exercise was expressed as the increase in cardiac output in milliliters per minute for each 100 c c. increase in oxygen consumption (Table I Fig 2) A normal average response of about 650 ml per minute might be expected.[17] The subject with congenital heart block had an inadequate response to exercise even though his resting value was normal The average preoperative response in 7 patients was approximately half normal (305 ml per minute) The average response postoperatively following an average duration of chronic pacing of 34 weeks was but little improved

A significant improvement was seen in one patient, G B but the absolute value was still subnormal. This subject noted subjective improvement in his strength and exercise tolerance. A longitudinal hemodynamic profile was available in this subject and is shown in Fig 3 Cardiac output in liters per minute is represented by the solid bars (Fig 3) The stroke volume corresponding to that output is represented by the cross-hatched bar for each pair of values. This patient was studied on 3 separate occasions, twice preoperatively and once postoperatively On June 17 1964 his idioventricular rate was 30 at both rest and exercise. At rest, the cardiac output was markedly diminished (3 4 L. per minute)

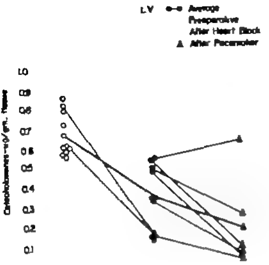

Fig. 4. The concentration of catecholamines in micrograms per gram of the left ventricular muscle are shown for individual normal dogs, for dogs 2 weeks after surgical production of complete heart block, and for dogs with chronic complete heart block 2 weeks after continuous pacing of the left ventricle. Dogs which served as their own controls are indicated as symbols which are connected by straight lines. The heavy black line connects symbols which represent average values. The left ventricular concentration of catecholamines averaged 0.659 μg per gram, ± 0.037 S.E. in normal control dogs, 0.342 μg per gram, ± 0.056 S.E. after 2 weeks of complete A-V block, and 0.203 μg per gram, ± 0.096 S.E. following an additional 2 weeks of continuous electrical pacing of the left ventricle.

even though the stroke volume was 110 ml. per stroke. The increase in cardiac output with exercise was inadequate although the stroke volume was increased to 160 ml. Five days later, the resting measurements were repeated and comparable values for cardiac output and stroke volume were obtained. With acute electrode catheter pacing at rates of 50 and 80, the cardiac output was increased to normal levels as the stroke volume progressively fell. Later that day, a permanent pacemaker was implanted. The patient was restudied 84 weeks later on March 18, 1966. His paced ventricular rate was now 72. The cardiac output during supine rest was virtually identical to the preoperative value in this 40-year-old man. His cardiac output response to exercise at 2 and 3 m.p.h. was improved over preoperative values although compared to normal individuals was still inadequate. Since he was unable to increase his fixed ventricular rate, stroke volume increased from a low resting value of about 50 to 110 ml. where it plateaued. He was unable to increase his stroke volume with exercise postoperatively to levels achievable with exercise preoperatively when the heart rate was 30. The resting stroke volume postoperatively was less than that found during acute electrode pacing preoperatively at a comparable ventricular rate.

The mean catecholamine concentration of the left ventricular muscle in the group of 11 normal dogs was 0.659 μg per gram tissue (± 0.037 S.E., range 0.480 to 0.851). Following 2 weeks of complete A-V block in a group of 10 dogs, the mean concentration was 0.342 μg per gram (± 0.056 S.E., range 0.143 to 0.550). The difference in mean left ventricular catecholamine concentration between the 2 groups was highly significant ($p < 0.001$). With continuous pacing of the left ventricle for an additional 2 weeks, a further decrease in the mean concentration was noted in a group of 6 dogs (mean 0.203 ± 0.096 S.E., range 0.043 to 0.650). The difference in mean left ventricular catecholamine concentrations between dogs with heart block who were chronically paced and normal dogs was highly significant ($p < 0.001$). If all 10 dogs with complete heart block were compared with the 6 dogs who were chronically paced, the fall in ventricular catecholamine concentration was not significant ($p < 0.2$). However, in the 6 dogs with complete heart block who served as their own controls, the myocardial catecholamine concentration decreased in 5 with chronic electrical pacing. Student's t test was applied to a paired comparison of ventricular catecholamine concentration in these 6 dogs. The mean catecholamine concentration following 2 weeks of complete heart block was 0.433 μg per gram (± 0.07 S.E., range 0.152 to 0.550) and following 2 weeks of pacing was 0.203 μg per gram (± 0.096 S.E., range 0.043 to 0.650). The decrease in left ventricular catecholamine concentration secondary to continuous electrical pacing for 2 weeks in these 6 dogs was statistically significant ($p < 0.01$). The mean left ventricular catecholamine concentration in 4 normal dogs paced at a rate of 135

for 5 to 7 days was 0.281 μg per gram of tissue (±0.121 S.E. range 0.056 to 0.590). The decrease in mean left ventricular catecholamine concentration in this group of paced normal dogs that was compared with the group of normal dogs that were not paced was significant ($p < 0.01$). In sham operated dogs left ventricular catecholamine concentration averaged 0.53 μg per gram (± 0.036 S.E. range 0.494 to 0.567). In one dog in whom muscle samples were obtained 2 and 4 weeks after production of complete heart block there was no further decrease in catecholamine concentration after 2 weeks; the values were 0.152 and 0.256 μg per gram of tissue, respectively.

Discussion

There are very few reported studies of cardiac output in patients with chronically implanted pacemakers. Physicians have assumed that the increased cardiac output during acute pacing is maintained following implantation of a permanent pacemaker. Benchimol[1] has examined the effect of exercise and drugs in patients with permanent pacemakers. Of interest, the average cardiac index in his patients was comparable to that found in this study, e.g., about 2.0 L. per minute per square meter.

Hence, although the cardiac index is significantly increased during acute pacing,[2-4] this increase is not maintained. A fall to prepacemaker levels was found as early as one week in one of our patients, R. Le, in whom a permanent transvenous electrode catheter was introduced into the right ventricle.

Several possible explanations for this apparent paradox must be considered.

There is no reason to suspect clinically intervening or progressive heart disease in these patients on the basis of history, physical examination, or laboratory tests.

It has been shown in dogs with complete heart block that the pacemaker site and the sequence of ventricular activation may induce profound differences in cardiac output.[3] The differences in cardiac performance when the heart is paced from various pacemaker sites has been explained by varying degrees of asynchrony during ventricular systole. In general, however, higher cardiac outputs were achieved from left ventricular pacemaker sites than from sites in the right ventricle.[14] It seems unlikely that a difference in pacemaker site could explain the results, since the right ventricle was paced prior to surgery and cardiac outputs rose whereas the left ventricle was paced by the permanent pacemaker in 16 of 17 subjects and yet cardiac outputs fell.

The possibility that chronic electrical pacing of the left ventricle could cause a significant reduction in myocardial catecholamines and in left ventricular performance was examined in a series of experiments in normal dogs and dogs with complete A-V block. We have confirmed the findings of Kaiser and colleagues[15] who showed that in dogs with experimental heart block there were significant decreases in myocardial catecholamine concentrations. We have shown that with chronic pacing of the left ventricle in dogs with complete heart block there was a further fall in ventricular catecholamine concentration to an average value of 0.21 μg per gram. Whether a low catecholamine store contributes to the low cardiac index in the patient with complete heart block or the patient who has been chronically paced is conjectural. Gaffney and co-workers[16] have shown that myocardial stores must be reduced to very low levels before the ventricle loses its responsiveness to sympathetic stimulation. These authors demonstrated that reserpine reduced the positive chronotropic response to cardioaccelerator nerve stimulation only after atrial norepinephrine concentrations have been reduced below 0.3 μg per gram.

Perhaps the simplest and most reasonable explanation for the findings is the effect of a change in heart rate itself. In normal untrained individuals, a change in heart rate is the most important mechanism for effecting rapid changes in cardiac output. In patients with complete heart block who are acutely paced with an electrode catheter the cardiac output increases and the stroke volume decreases as the heart rate is increased from a slow idioventricular rate.[2-4] In most patients an optimal rate can be found at which the cardiac output is maximum and above which it falls. In addition

to the rise in cardiac output induced by an increase in heart rate itself there is evidence that a more rapid heart rate may increase myocardial contractility The mechanism responsible for this effect is not clear but was first described by Bowditch.[17] He found that an increase in heart rate caused a stepwise ("treppe") increase in contractility Sarnoff and Mitchell[18] have invoked the Bowditch effect to explain the potentiation of contractility seen following extrasystolic beats, after electrical stimulation of heart muscle and with paired stimulation. It seems reasonable to assume that during chronic pacing at the same increased rate the initial increase of contractility and cardiac output (Bowditch effect) is lost and the cardiac index returns to its prestimulation value.

This study has certain clinical implications. The primary indication for implantation of a permanent pacemaker in a patient with complete heart block is one or more Adams-Stokes attacks. Surgical intervention solely to improve cardiac output in the patient with chronic acquired complete heart block, who has never had an Adams-Stokes seizure and is not in clinical heart failure seems unwarranted on the basis of this study In all but one of our patients, failure was lacking despite their low cardiac outputs. Inferences regarding permanent pacemaker implantation cannot be applied from this study to patients with gross congestive heart failure, severe cerebral hypoxia, or uremia secondary to decreased renal blood flow Indeed the value of increasing the heart rate with pacemakers in these relatively uncommon patients has been clearly demonstrated.[illegible]

On the basis of this study and the earlier findings of Kaiser and colleagues[illegible] there is evidence that myocardial catecholamine concentrations are significantly decreased in dogs with complete heart block and may be further decreased with chronic electrical pacing In the absence of measurements to the contrary in humans with heart block, it would seem judicious to avoid the use of reserpine or other drugs which deplete myocardial catecholamine stores in such patients. Even if the catecholamine deficient heart is not wholly responsible for the low cardiac output observed its response to sympathetic nervous activity may be impaired

Summary and conclusions

The low cardiac output of patients with chronic acquired complete A V block is usually increased during temporary ventricular pacing at a rate of 60 to 90 with an electrode catheter It is generally assumed that this improvement is maintained following implantation of a permanent pacemaker This has not been our experience.

Cardiac output was measured by an indicator-dilution technique in 17 adult patients (ages 46 to 79 years) with acquired complete heart block during supine rest and treadmill exercise to exhaustion. Studies were repeated during chronic pacing an average of 34 weeks after implantation of a fixed-rate ventricular pacemaker (range, 1 to 88 weeks)

The average resting control cardiac index was low (2 0 L. per minute per square meter rate 36) With chronic pacing the resting cardiac index was unchanged from control (2.0 L. per minute per square meter rate 75) Before pacing the increase in cardiac output with exercise was low (305 ml per minute per 100 c.c. O_2 consumption) The cardiac output response to exercise was but little improved postoperatively (336 ml. per minute per 100 c.c. O_2 consumption) and the stroke volume was lower than preoperative levels at rest or exercise

In dogs, mean left ventricular myocardial catecholamine concentrations were significantly reduced (0 342 μg per gram $\pm$ 0 056 S.E. normal 0 659 μg per gram $\pm$ 0 037 S.E.) 2 weeks after surgically induced complete heart block and were further reduced after 2 weeks of electrical pacing (0.203 μg per gram $\pm$ 0 096 S.E.) Whether these findings apply to man with complete heart block is uncertain at this time.

REFERENCES

1 Segal, N Hudson, W A., Harris, P and Bishop, J M The circulatory effects of electrically induced changes in ventricular rate at rest and during exercise in complete heart block, J Clin. Invest. 43:1541 1964.
2. Sowton E. Hemodynamic studies in patients with artificial pacemakers, Brit. Heart J 26 737 1964.
3 Benchimol, A., Li, Y and Dimond, E. G.,

Cardiovascular dynamics in complete heart block t arious heart rates Effect of exercise t a fixed bea t rate Circulation 30:542, 1964

Benchimol, A Li, Y Dimond, E. G., Voth, R B and Roland A S Effect of heart rate, exercise and nitr glycerine on the cardiac dynamics n complet heart block, Circulation 28:510 1963

5 Bevegard, S Observations on the effect of arying ventricular rate on the circulation t rest nd during exercise in ra patient with an artificial pacemaker Acta med Scandinav 172:615 1962

6 Stewart H J Deitrick, J E Crane N F nd Thompson W P Studies of the circulation in presence of bnormal cardiac rhythms obser tions relating t h thms ssociated with rapid entric la r t nd to rhythms associ ted w th low ventricula rate J Clin Invest 17:449 1938

7 Hamilton W F Moore J W K nsman, J M and Spurling R G Studies on the circulation. IV Further analysis of the injection method, and of changes in hemod namics under physiological and pathological cond tions, Am J Physiol. 99:534 1932

8 Scholander P F Analyzer for accurat estimation of respiratory gases one-half cubic centimeter samples, J Biol Chem 167:235 1947

9 Crout J R Creveling C R nd Udenfriend, S Norepinephrine metabolism in rat brain nd heart J Pharmacol & Exper Therap 132:269 1961

10. Gaffney T F Burket R L nd Woronkow S C techolamine ontent f the pregnant and nonpregna t huma uterus, Obst & Gynec 25:340 1965

11 Brandfonbrener M Landowne M and Shock, N W Change in ardiac outpu w th age, Circ lation 12 55 1955

12. Altman, P L. Handbook of circulation, Philadelphia, 1959 W B Saunders Co., page 74.

13. Benchimol, A Cardiac functions during electrical atimulation of the heart. Effect of exercise and drugs in patients with permanent pacemakers, Am J Cardiol 17:27 1966.

14 Lister J W Klotz D H Jomain, S L Stuckey J H and Hoffman, B F Effect of pacemaker sit on cardiac output and ventricular activation in dogs with complete heart block, Am. J Cardiol. 14:494 1964

15 Kaiser G. C., Jellinek, M Cooper T and H nlon, C R Experimental heart block effect on myocardial catecholam ne concentration, Am. J Physiol. 208:477 1965

16 Gaffney T E Chidsey C. A and Braunwald, E. Study of the relationship between the neurotransm tter tore nd adrenergic nerve block induced by reserpine and guanethidine, Circulation Res 12:264 1963.

17 Bowd tch H P Ueber die eigenthumlichkeiten der reizbarkeit welche die muskelfasern des herzens zeigen Beitr d k. sachs, Ges. d. Wiss. 23:652, 1871

18 Sarnoff S. J and Mitchell, J H The regulation of the performance of the heart, Am. J Med. 30 747 1961

19 Muller O F nd Bellet, S. Treatment of intractable heart failure in the presence of complet trioventricular heart block by the use of the internal cardiac pacemaker New England J Med. 265 768, 1961

20. Friedberg C. K Donoso, E Stein W G Kahn, M and Litwak, R The role of bradycardia in the retention of sodium and water in complete heart block with nd without heart failure i human beings, AM HEART J 69:293 1965

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julian Frieden

Surgical treatment of valvular heart disease

Part VII. Prosthetic cardiac valves

PROGNOSIS AND MANAGEMENT

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The development of the prosthetic mitral ball valve by Starr and Edwards in 1961 was a milestone in the surgical treatment of acquired valvular disease. Routine replacement of cardiac valves became possible with this development for the first time. The striking improvement in patients with severe cardiac failure following prosthetic valve replacement quickly led to their widespread use. By 1967 Starr stated that over 15,000 mitral prostheses had been sold by the Edwards Laboratories.

Enthusiasm has been tempered with caution, however, because of the distressingly high incidence of thromboembolism, a frequency approaching 30 per cent with earlier prostheses. Thrombi tend to form at the junction of autogenous tissue with the metallic surface of the valve. Intensive investigation of different types of valves, including different ball valves, disc valves, and other designs, has not led to any significant improvement in the incidence of thromboembolism. A recent significant development has been the introduction of valves completely covered with porous Teflon cloth to permit total coverage of the valve surface with autogenous tissue. Such valves first became available for limited clinical trial about a year ago and have been widely adopted because the incidence of thromboembolism appears to have been reduced from 20 to 30 per cent to about 2 to 3 per cent, a tenfold reduction.

With the hazards of thromboembolism, prosthetic valve replacement has usually been employed only for patients disabled with progressive congestive failure. This cautious policy has, of course, limited operation to patients with advanced cardiac disease. It should be emphasized, however, that patients seldom progress to a stage where operation is futile. Even patients in advanced Class IV cardiac failure tolerate operation surprisingly well, admittedly with a higher operative mortality rate, but striking improvement is often obtained. This point deserves emphasis because patients are still frequently seen in whom operation has been considered futile because of far-advanced cardiac failure.

At present, however, it is not known how many symptoms of advanced cardiac disease can be eliminated with the insertion of a prosthetic valve. A small percentage of patients with chronic congestive failure from mitral stenosis still fail to

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improve following operation The prognosis is also uncertain for patients with severe cardiac enlargement (cardiac weight 700 to 800 Gm) from aortic insufficiency With the development of safer prostheses, operations in the future will probably be employed at an earlier stage in cardiac disease, but at present the exact degree of improvement cannot be predicted with certainty for any specific patient Hence operative insertion of a prosthetic cardiac valve should be considered as only one phase in the management of the patient with cardiac disease. Improvement in cardiac function will surely occur varying from a small change to complete elimination of any signs of congestive failure. Close observation is needed however not only to evaluate the degree of improvement but also to determine the function of the prosthesis and to detect any signs of thromboembolism The importance of careful management is emphasized by the fact that the mortality rate within two years following discharge from the hospital after aortic or mitral valve replacement may equal or exceed the operative mortality rate Some of the deaths are due to malfunction of the prosthesis, but others are due to arrhythmias or congestive failure. Careful medical management of a patient may significantly reduce this distressingly high late mortality following successful implantation of a prosthetic valve. In the following paragraphs, some of the more important complications following prosthetic valve replacement will be emphasized.

Complications following prosthetic valve replacement

Anticoagulation and thromboembolism. The usual policy following prosthetic valve replacement, including that of the author is to maintain anticoagulant therapy permanently for the hazards of thromboembolism continue even three to four years following operation The author's policy is to initiate therapy with heparin four to five days after operation, and subsequently maintain anticoagulation with sodium warfarin keeping the prothrombin time about twice the normal range. This usually requires between 5 and 10 mg. of sodium warfarin daily Hopefully the new cloth-covered prostheses should be covered with autogenous tissue within six months. Anticoagulation in such patients has been cautiously stopped by some investigators within a year after operation but significant data are not yet available.

Anticoagulation of course, is not free of hazards and requires both careful supervision by the physician and close cooperation of the patient. In the past 2½ years, during which over 350 mitral and aortic replacements have been performed there has been at least one fatality from intracranial hemorrhage from sodium warfarin, due to the unfortunate refusal of the patient to maintain close contact with his physician. Significant gastrointestinal hemorrhage has occurred in several patients, in two of whom it was necessary to stop sodium warfarin because of recurrent gastrointestinal bleeding despite a prothrombin time only slightly above normal range.

Thrombi dislodged from a prosthetic valve are usually small and undoubtedly many of them are never recognized. Occlusion of a major artery such as the femoral or popliteal is unusual. Cerebral emboli are, of course, the most hazardous. Some patients may complain of momentary episodes of dizziness or confusion but no neurological abnormalities are detectable.

When a cerebral embolus occurs, the level of anticoagulation should be carefully noted as a guide to future therapy Heparin therapy is preferred following thromboembolism partly because of the ease of control and partly because heparin may be more effective in preventing further emboli Often a cerebral embolus occurs only as an isolated episode without any statistical likelihood that further emboli will occur Full recovery follows in most patients, but large emboli may be disabling or fatal. As stated earlier the data thus far available from reports on the new cloth-covered prostheses indicate that the risk of embolism has been reduced to about one tenth of that with earlier prostheses. In April, 1968 Braunwald and Morrow[4] reported that only one embolus had occurred following 55 valve replacements with cloth-covered valves and Beall had recognized only two emboli after 106 re-

placements. Hopefully these encouraging results will be sustained with additional experience.

Prosthesis malfunction. A perivalvular leak about the rim of a prosthetic valve is the most frequent complication. This is most common after mitral valve replacement, occurring in perhaps 10 to 15 per cent of patients. It usually results from sutures gradually cutting through the residual annulus of the valve, the difficulty resulting from inadequate strength of the fibrous tissue in the annulus. Dislodgement is often a gradual process as a result of repeated stress on the valve, as the valve settles in the valve ring over millions of cardiac cycles. Signs of leakage may not become evident for several months after operation.

There is great variability in the amount of fibrous tissue in the mitral annulus among different patients, perhaps resulting from variation in the severity of the previous rheumatic inflammatory process. In some patients, dense scars are present, while in others the tissues are unusually fragile. The incidence of leakage has gradually been reduced by improvements in operative technique, the trend being to employ a large number of sutures, often buttressed with Teflon felt.

Detection of a significant leak about a mitral prosthesis may be surprisingly difficult. A systolic murmur may or may not be audible. Often the only clinical finding is a persistent limitation of cardiac function, perhaps with signs of right-sided failure. The diagnosis can be established by cardiac catheterization, finding an elevation of the left atrial pressure. Subsequent confirmation of the diagnosis can be done only by left ventricular angiography demonstrating reflux of dye into the left atrium. Once the diagnosis has been established reoperation to suture the area of leakage, often only 2 to 4 mm. in diameter can usually be successfully performed.

Leakage about an aortic or tricuspid prosthesis is unusual. In the aortic area, the annulus is better developed than in the mitral area while a tricuspid valve is subjected to much lower pressure during cardiac contraction than is an aortic or mitral prosthesis.

A thrombus developing on the prosthetic valve, causing restriction of motion of the ball and obstruction of the valve orifice, is an unusual but lethal complication if unrecognized. Several years ago this author treated a patient who shortly following pregnancy developed massive thrombosis of the entire mitral valve. She has, interestingly enough, remained free of complications in the three years following surgical replacement of the prosthesis with another ball valve prosthesis.

The development of erosion or fracture of a Silastic ball, termed "ball variance," is a significant and often lethal complication of aortic prostheses, but is fortunately almost unknown with mitral prostheses. This disappointing and disastrous complication of the Silastic ball led to the prompt development of a hollow metal ball introduced about a year ago and now uniformly employed in both aortic and mitral prostheses. Hence, ball variance should disappear but must be closely watched for in the many patients currently with a functioning Silastic ball prosthesis.

The complication has been most frequent when some difficulty occurred at the original implantation of the prosthesis, probably from inserting the valve in a distorted position which prevented free spinning of the ball and subsequently resulted in unequal wear of the surface. Different types of catastrophes have resulted either fracture of the ball with fatal aortic insufficiency or dislodgement of the ball from the cage and embolization into the peripheral circulation. At autopsy such dislodged balls have been found at the bifurcation of the abdominal aorta.

Several signs may warn that ball variance is developing. The most ominous of these is the sudden appearance of a low-grade diastolic murmur. Starr emphasized that a variation in the intensity of the normal click produced by seating the ball in the prosthetic cage warns of ball variance. It has been suggested that serial phonocardiograms be obtained every six months following operation for comparison of changes in the intensity of the click. The appearance of anemia or other signs of hemolysis are also warning signs. If reasonable suspicion exists that ball variance is occurring, reoperation should be

employed promptly for replacement of the prosthesis.

One such patient in whom the only signs were a slight diastolic murmur and anemia was recently operated upon at the author's Cardiovascular Service. At operation erosion with impending fracture of the Silastic ball was found.[5]

Cardiac failure. As mentioned earlier the degree of improvement following mitral or aortic replacement varies widely. In 1967 Starr reported experiences with a group of 278 patients undergoing mitral valve replacement. Sixty-five per cent of the patients were subsequently free of all cardiac symptoms, 25 per cent had mild restriction of exercise, while 10 per cent had persistent cardiomegaly and required permanent intensive medical therapy. In 76 patients surviving mitral valve replacement reported by Morrow,[7] 47 were classified as Class I, 26 as Class II, and three as Class III. For unknown reasons, the frequency of continued impairment of cardiac function has been greater after a mitral valve replacement than after an aortic operation.

The unpredictable variation in the degree of improvement following operation emphasizes the need for careful serial medical observation. The degree of cardiac enlargement before operation, as compared to the amount of decrease in heart size after operation, is probably the most useful objective sign of improvement. This can be correlated with signs of ventricular hypertrophy on the cardiogram, a particularly useful guide in patients following aortic valve replacement. Following mitral valve replacement the tolerance for sodium must be carefully evaluated for several months, because some patients promptly develop edema with an unrestricted salt intake. The author's usual policy is to increase gradually physical activity over a period of several months following operation, noting the presence of symptoms, reduction in heart size, and the need for salt restriction.

If cardiac failure persists following operation there are at least ten different possibilities which should be evaluated. The most important of these, and perhaps the most difficult to detect, is a *leak about the prosthesis*. Obstruction of the prosthesis from a *thrombus* is rare. With multivalvular disease, the possibility of symptoms arising from significant *disease in other valves* should be considered, such as residual tricuspid insufficiency following mitral valve replacement. It should be emphasized that both the operative mortality rate and the subsequent risk of thromboembolism is almost identical following multiple valve replacement as following isolated aortic or mitral replacement. Hence the trend at present is to employ freely multiple valve replacement at the time of operation if significant disease is present in more than one valve.

Residual pulmonary hypertension is very rarely a cause of persistent disability even though pulmonary systolic pressure may have been greater than 100 mm. Hg before operation in a patient with severe mitral stenosis. *Pulmonary embolism* is another possibility which is rarely found.

In the first few weeks after operation a *recurrent pericardial effusion* has been observed in a few patients, often developing to a severe degree before detection. Normally an effusion is unusual because the pericardial space is obliterated by fibrin following operation. Also in the first few weeks following operation a *recurrent pericarditis* (the so-called pericardiotomy syndrome) can be a troublesome cause of persistent fever, friction rub, and pleural effusion. Steroid therapy is usually promptly effective, but some patients have had continuous difficulty for as long as three to four months following operation.

When fever persists following operation or recurs after discharge from the hospital the grave possibility of *endocarditis* on the prosthetic valve must be considered and excluded by serial blood cultures. The usual differential diagnosis is between pericarditis and endocarditis. Fortunately pericarditis is almost always found to be the cause. The detailed treatment of endocarditis will not be discussed here, but often this is a fatal complication when it occurs. With care, however, such a disastrous complication can usually be avoided. With the intensive use of antibiotic therapy the author's cardiovascular group has had only one fatal endocarditis in the past six years. Starr has reported similar experiences.

Serious arrhythmias such as atrial fibrillation or other atrial arrhythmias can in themselves precipitate serious cardiac failure to a fatal degree. In the past few months, two patients have been admitted several months following multiple valve replacement each in near lethal congestive failure with gross edema. In both a serious, uncontrolled arrhythmia, in association with extensive intake of sodium was the only disability found. Prompt recovery ensued after intensive therapy.

Finally the unfortunate possibility of *intrinsic disease of the left ventricular muscle* either from coronary artery disease, rheumatic fever or unknown causes must be considered. Such a diagnosis should be carefully established usually by finding elevation of the left ventricular diastolic pressure about 15 mm Hg at cardiac catheterization. Starr has reported that 10 per cent of patients undergoing mitral valve replacement show little or no benefit from operation and presumably have cardiac failure from muscle disease. Similarly in about one half of patients who have died in the first two years following operation no satisfactory anatomical cause of death has been found, but only scattered areas of fibrosis in the left ventricle. Presumably death was due to an arrhythmia, but the cause of the fibrosis, either rheumatic or otherwise, is unknown. Hopefully careful management of such patients might prevent the development of fatal arrhythmias. Sudden death has occurred in some patients following aortic valve replacement usually in patients with extreme degrees of left ventricular hypertrophy after operation. Again these deaths are presumably due to arrhythmias, for a postmortem examination has not found a satisfactory cause of death. In the future such patients will probably be operated upon at an earlier stage of their cardiac disease.

Prophylaxis from infection. A patient with a prosthetic valve has an increased susceptibility to the development of bacterial endocarditis during periods of transient bacteremia, such as that seen following a dental extraction. This susceptibility is similar to the well-known increased susceptibility in patients with valvular disease from rheumatic fever. Appropriate prophylactic antibiotic therapy should be given for a short period of time before and after elective surgical procedures.

Homografts for aortic valve replacement. At present there is intensive investigation of homograft aortic valves instead of prosthetic ones. A detailed discussion of homograft valves is beyond the scope of this report, but extensive experience with aortic homograft prostheses by several groups has found good valvular function without any thromboembolic complications. However there is a distressingly high frequency of aortic diastolic murmurs following operation which may be a warning of future development of aortic insufficiency. Recently some investigators have used inverted aortic valve homografts for mitral valve replacement but only preliminary information is yet available.[6] In addition other groups have made initial studies with replacement of the mitral valve with pericardium or the aortic valve with fascia lata, but only limited data are available.

Summary

Prosthetic valve replacement may be performed in virtually any patient with valvular heart disease, regardless of the severity of his congestive failure. Despite a successful operation there has been a late mortality rate occurring one to two years after operation, in about 10 per cent of patients. This has been due to several factors reviewed in this article, including thromboembolism, prosthesis dysfunction and persisting residual of cardiac disease. The importance of careful medical management following operation has been emphasized for by precise management the risk of these complications may be lessened. The critical question in the future is whether the striking decrease in thrombus formation with the new cloth-covered prostheses will be confirmed by future experience. A major question subsequently to be decided is whether the improved prosthetic valves will remain preferable over different types of homograft or heterograft valves.

REFERENCES

1. Spencer F C., Cortes, L. Mascarenhas, L., and Koepke, J., The mechanism of thrombus forma

tion upon the Starr Edwards prosthetic mitral valve A n. Surg 165:814 1967
2. Braunwald, N S. and *Bonchek, L. I.: Prevention* of thrombus formation on rigid prosthetic heart valves by *ingrowth* of autogenous tissue, J Thoracic & Cardiovas. Surg 54:630, 1967
3 Braunwald, N S., and Morrow A. G Tissue ingrowth and the rigid heart valve review of clinical and experimental experience during the past year J Thoracic & Cardiovas. Surg In press.
4 Spencer F C Trinkle, J K and Reeves, J T Successful replacement of thrombosed mitral ball-valve prosthesis, J A M A. [illegible] 1249 1965.
5 Scalabrini, B Y Rader B Milano, H., and Clauss, R. H: Successful replacement of defective ball of prosthetic aortic valve J. A. M A. *203:335 1968.*
6. Starr A. Herr R. H and Wood, J A. Mitral replacement; review of six years experience J Thoracic & Cardiovas. Surg 54:333 1967
7 Morrow A. G Oldham H. [illegible] Elkins, R. C., and Brau wald E. Prosthetic replacement of the mitral valve preoperative and postoperative clinical and hemodynamic assessments of 100 patients, Circulation 35:962, 1967
8. Angell, W W Iben, A. B Stinson, E. B., and Shumway N E. Fresh aortic homografts for multiple valve replacement J Thoracic & Cardiovas. Surg In press.

Annotations

Heart and coronary artery disease in hypothyroidism

Zondek and Fahr[4] were the first to describe specific cardiac changes in myxedema slow indolent heart action, dilatation of the heart, and low electrocardiographic complexes. This condition, for which they coined the term "myxedema heart," was completely reversible after substitutive therapy

The causative relationship between myxedema and coronary artery disease, a more recent concept based on clinical and pathological evidence, is actually questioned on several grounds.

The frequency of angina pectoris in myxedema contrasts with the relatively rare occurrence of myocardial infarcts and under thyroid therapy anginal pains may either improve or become worse.

From these observations, controversy arose about the origin of angina pectoris in myxedema and its relationship with coronary atherosclerosis.

The "myxedema heart" and the atherogenic effect of hypothyroidism need further investigation and explanation. With this object, clinical observations were made on 87 patients and postmortem studies were performed on 25 patients the results were compared with those obtained from similar investigations performed in control subjects, matched for sex, age, and extrathyroid pathological conditions (diabetes, obesity and hypertension)

Cardiac silhouette is generally described as increased in size in hypothyroidism This has been attributed to several causes acting separately or in combination dilatation of cardiac cavities, myocardial hypertrophy myocardial edema, fibrous tissue replacement, and pericardial effusion

The main pathological data are summarized in Tables I and II They show the great frequency of an increase in the weight of the heart and its association with left ventricular hypertrophy and myocardial edema. Hypertension seems to be associated only with moderate hypertrophy (300 to 400 grams in 7 out of 10 cases). Pericardial effusion is less frequent and is associated with ventricular hypertrophy This is also true for left ventricular dilatation

A characteristic electrocardiographic pattern has been described in myxedema. From Table III appears that bradycardia, low voltage and disturbances in atrioventricular conduction are often observed in hypothyroid patients. The frequency of myocardial ischemia in the myxedematous subjects contrasts with the finding of an equal number of heart infarcts in both groups. Recently Cohen and Lloyd-Thomas showed that in untreated myxedema, the exercise electrocardiogram (ECG) of an [illegible] shows an ischemic pattern. After thyroid therapy this alteration usually disappears, and the authors concluded that the responsible myocardial anoxia is not due to coronary atherosclerosis but to a metabolic alteration of the heart muscle The disappearance of those ischemic signs under treatment may be put together with the possible disappearance, following the same therapy of angina pectoris in myxedema. More frequently however pre-existent anginal pains become worse or appear [illegible] after thyroid replacement therapy

Admittedly angina pectoris in hypothyroidism may have a twofold origin. One is related to the [illegible] proved atherosclerotic changes in the coronary arteries thyroid therapy may increase its severity and even induce myocardial infarcts. [illegible] origin may reside in myocardial edema [illegible] the increase in heart size and weight (Table II [illegible] It may be explained by the increased capillary [illegible] meability described in myxedema. It is [illegible] that these are the anginal pains that [illegible] disappear under therapy [illegible]

The relationship between myxedema and coronary artery disease is actually much [illegible] tion Many authors raise objections [illegible] based on several grounds.

1 Autopsy reports of spontaneous [illegible] usually concern patients over [illegible] period of life in which spont[illegible] is almost universally present.[illegible]

2. Patients in whom hypothyroid[illegible] induced for the treatment [illegible] pains do not, after their [illegible]

Table I Pathology of the heart [illegible] autopsied cases

Mean weight	
Left ventricle hypertrophy [illegible] the wall > 14 mm	[illegible]
Left ventricle dilatation	
Pericardial effusion	
Myocardial edema	
Coronary atherosclerosis	
Myocardial infarct	

Table II Correlations between heart weight and pathological findings

Weight	Pericardial effusion	Left ventricle dilatation	Left ventricle hypertrophy	Hypertension	Myocardial edema	Coronary atherosclerosis
270	−	−	−	−	−	+
275	−	−	−	−	−	−
300	−	−	+	−	−	+
310	−	−	+	+	−	−
315	−	−	−	+	−	+
330	−	−	+	−	+	+
340	−	−	−	+	−	+
350	−	−	+	−	−	+
360	−	+	+	−	−	−
360	−	+	−	+	−	+
360	+	+	+	+	−	+
380	−	−	+	+	−	+
390	−	−	+	−	−	+
400	−	+	+	+	+	+
420	+	−	+	+	+	−
430	+	−	+	−	−	+
450	−	−	+	−	+	+
450	−	−	+	−	+	+
450	−	+	+	+	+	+
480	+	−	+	−	+	+
490	+	−	+	−	+	+
535	−	+	+	+	+	+
540	+	−	+	−	+	+
560	+	−	−	−	+	+
610	+	+	+	−	+	+
25	8	7	19	10	12	21

Table III ECG's in 56 cases of myxedema and in 56 matched controls

	Myxedematous patients	Controls
Normal	3	16
Nonspecific myocardial alterations	24	27
Low voltage	28	4
Bradycardia	11	6
Disturbances of atrioventricular conduction	10	1
Disturbances of intraventricular conduction	5	4
Ischemia	6	0
Myocardial infarct (old and recent)	9	8
Left ventricular strain	9	6

atherosclerosis beyond a normal degree for their age.[illegible]

3. Hypertension, frequent in myxedema,[12,14] may play a role in the development of coronary atherosclerosis.[13]

In the present study the mean age is 66.5 years for the still living myxedematous subjects and 70.4 years for the autopsy cases. This is in contrast with the mean age of the younger patients studied by Blumgart and associates.[11] However when patients are matched for sex, age, and extrathyroid pathology with nonmyxedematous subjects, neither age, nor hypertension can play a great part in the differences found in the degree of coronary atherosclerosis between the two population groups (Table IV). This last table confirms the classical concept of the atherogenic effect of thyroid deficiency. Keating and colleagues[14] pointed out the scarceness of myocardial infarcts in myxedema, if compared with the severity of coronary atherosclerosis in this condition. This study confirms their observation. Indeed, anoxic ECG's are frequent (Table III) but, except under therapy there is no increased incidence of myocardial infarcts in myxedema (Tables III and IV).

This contrast illustrates the immediate protective effect of hypothyroidism on the heart. This organ benefits from reduced metabolic needs and reduced activity: therefore, it can resist the relatively anoxic state imposed by coronary atherosclerosis. Moreover, this protective effect has two other facets: (1) That hypertension tends to be reduced in the course of hypothyroidism has been observed in man as well as in the rat[14]; this may be explained, at least partly, *by reduced sensitivity to catecholamines.* (2) A state of blood hypocoagulability is often present in myxedema.[15] Thus myxedema has

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Table IV Coronary atherosclerosis and infarcts in necropsies of myxedematous subjects and controls

	Myxedematous patients (20 females—5 males)				Matched control (40 females—10 males)			
	Coronary atherosclerosis (N*)			Myocardial infarct	Coronary atherosclerosis (N*)			Myocardial infarct
Degree	0	I	II		0	I	II	
No. of subjects	1	3	21	6†	20	7	23	3
Incidence (%)	4	12	84	24	40	14	46	6

*Degree I moderate atherosclerosis with only lipid deposits. Degree II severe atherosclerosis with marked narrowing of the lumen.
†In four cases, thyroid therapy had been given shortly before death.

an ambiguous action on the heart it induces coronary atherosclerosis, but protects against the consequences of this atherosclerosis.

The demonstration of causative relationship between hypothyroidism and coronary artery disease contrasts with the data from Blumgart and associates.[12] This discrepancy is probably to be explained by fundamental differences between iatrogenic hypothyroidism and spontaneous myxedema. Spontaneous myxedema is indeed the end result of protracted process of atrophic asymptomatic thyroiditis, condition without clinical signs but with serological and metabolic alterations.[19] This state of premyxedema may be of major importance in the development of coronary artery disease.

Since this paper was written, Steinberg[20] published study on the same subject. Making difference between hypertensive and normotensive myxedematous patients, he found for the former significant increase in coronary atherosclerosis when compared with controls. That he did not find the same for the latter group may be due to the criteria used to assess hypertension.

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REFERENCES

1 Zondek, H Das myxoedemherz, München med Wchnschr 65 1180, 1918
2 Fahr G Myxedema heart J A M A 84:345 1925.
3. Means, J H The thyroid and its diseases, ed 1 Philadelphia 1937 J B Lippincott Company
4 Smyth C J Angina pectoris and myocardial infarction as complications of myxedema, Am. Heart J 15:652, 1938
5. Beaumont, G F and Robertson J D Angina pectoris in hypothyroidism Lancet 1:682, 1939
6. Douglass, R C and Jacobson, S. D Pathologic changes in adult myxedema survey of 10 necropsies, J Clin Endocrinol. 17 1354 1957
7 Vanhaelst, L Neve, P Chailly P and Bastenie, P A Coronary artery disease in hypothyroidism. Observations in clinical myxoedema, Lancet 2:800, 1967
8. Hamolsky M W Kurland, G. S and Freedberg, A. S. Current concepts in hypothyroidism, in Creppell, K. R., editor Oxford, 1963 Pergamon Press, Inc p. 133
9 Cohen, R D and Lloyd Thomas, H. G Exercise electrocardiogram in myxoedema, Brit. M J 2:327 1966.
10. Keating, F R J Parkin, P W Selby J B and Dickman, H S Treatment of heart disease associated with myxoedema, Progr Cardiovas. Dis 3:364, 1964
11 Lange K Capillary permeability in myxoedema, Am J M Sc 208:5 1944
12 Blumgart, H L Freedberg A S and Kurland G S Hypercholesterolemia, myxoedema and atherosclerosis, Am. J Med 14:665 1953
13 Hamilton, J D and Greenwood, W F Myxedema heart disease, Circulation 15:442 1957
14. Attaran, E Myxoedema and hypertension New York State J Med 63:2801 1963
15 Perera, G. A. The effect of antithyroid drug on the clinical course of malignant hypertension, Ann. Int Med. 33:29 1961
16 Demanet, J C Contribution à l'étude du rôle de la thyroïde dans l'hypertension expérimentale, Arscia Bruxelles, Ed 1966
17 Demanet, J C and Thys, J P I Actualités Endocrinologiques 7 série-L expansion Paris, 1966, p. 131
18. Egeberg, O Influence of thyroid function on the blood clotting system, Scandinav J Clin. & Lab. Invest. 15 1 1963
19 Bastenie, P A Neve P Bonnyns M Vanhaelst, L and Chailly P Clinical and pathological significance of atrophic asymptomatic thyroiditis, Lancet 1:915 1967

20. Fowler P B S. and Swale, J Premyxoedema and coronary artery disease, Lancet 1 1077 1967
21 Bastenie P A. Vanhaelst, L. and Neve, P Coronary artery disease in hypothyroidism. Observations in preclinical myxoedema, Lancet 2 1221 1967
22. Steinberg, A. D Myxedema and coronary artery disease, Ann. Int. Med. 68:338, 1968

Mortality trends for acute and chronic nephritis and infections of the kidney

Mortality data for renal disease are reported under groups of numbered rubrics of the seventh revision of the International Statistical Classification of Disease (ISC)[1] ISC 590-591 acute nephritis ISC 592 594 chronic nephritis and ISC 600 infections of the kidney Death rates for ISC 590-591 and 592 594 have been decreasing for at least the past two decades. In the United States age, race and sex specific death rates for chronic nephritis declined up to tenfold between 1940 and 1964 for both races at all ages. Age-adjusted rates decreased in a similar fashion in Western Europe (except Finland) Australasia, and Ceylon[2] between 1950 and 1960

The figure shows the age distribution of combined underlying and secondary deaths from renal disease for Caucasians of both sexes in the United States in 1955 The relative role of acute and chronic nephritis and infections of the kidney vary considerably with age, so in our analysis each category was treated separately (Fig 1).

In the United States between 1950 and 1964 crude death rates for acute nephritis declined by 70 per cent, and for chronic nephritis by 65 per cent. In contrast, deaths from infections of the kidney rose by 150 per cent. The same trends are found in data from England and Wales, where the values for the crude death rates are at the same level as in the United States. A possible interpretation of this is that, because of current interest in bacteriuria, some of what used to be called chronic nephritis is now termed infections of the kidney In Denmark[3] and Sweden increasing death rates from nonobstructive pyelonephritis were noted during the late 1950s which may be related to analgesic abuse in these countries. However nephropathy associated with chronic analgesic use has never been a major prob-

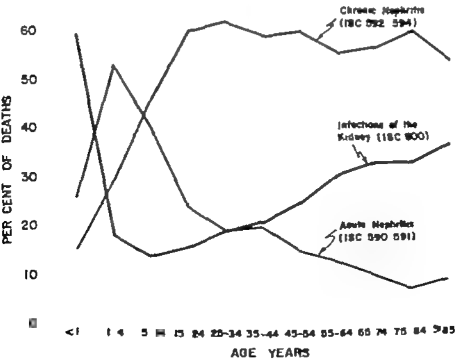

Fig 1 Percentage distribution, by age, of deaths in Caucasians from three subclasses of renal disease acute nephritis (ISC 590-591), chronic nephritis (ISC 592 594), and infections of the kidney (ISC 600) in 1955 (underlying and secondary causes combined).

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lem in the United States and probably does not explain our findings.

It was found from an analysis of multiple causes of death[4] that in 1955 the most prominent and statistically significant association between chronic nephritis as a secondary cause of death and any underlying cause was with diseases of the cardiovascular system. These disorders (ISC 330-334, 440-450) and diabetes mellitus accounted for 55.5 per cent and 6.7 per cent, respectively of the underlying causes of death with which chronic nephritis was associated. Between 1940 and 1955 the death rate from arteriosclerotic heart disease rose threefold while this was taking place, it would seem that chronic nephritis moved from underlying to secondary cause of death and is now appearing on certificates for which cardiovascular disorders, in particular arteriosclerotic heart disease are the underlying causes. In addition, it is likely that patients with diabetes who died of renal insufficiency have been increasingly classified as deaths from diabetes rather than chronic nephritis since, during the past three decades, nephropathy has become widely recognized as a manifestation of diabetes. The suggestion that there has been a movement from underlying to secondary cause is supported by the fact that the death rates for chronic nephritis as an underlying cause dropped nearly 90 per cent between 1940 and 1955 while the secondary cause rate hardly altered.

Analysis of the ratios of male-to-female death rates for chronic nephritis and infections of the kidney suggest another diagnostic change. The ratios for chronic nephritis increased between 1940 and 1964 at each decade from 35 to 44 to > 85 years; the increase was more marked at the younger ages. As the ratios changed while the death rates for both sexes were falling, a slower decline must have occurred in the death rates for men than women. Infections of the kidney show the reverse pattern in the age groups 35 to 44 and 45 to 54, which is consistent with the view that a proportion of the deaths that were previously coded under ISC 591-594 for women is now being coded under ISC 600—a diagnostic change rather than a real change in the mortality rate.

It has been estimated from mortality data that the eligibility rate for chronic intermittent renal dialysis would be 5.1 per 100,000 persons aged 15 to 55 in the United States. This rate agrees in magnitude with that found by Morrin in a prevalence study in Ontario, Canada, which, after adjustments for age fell between 4.2 and 6.5 per 100 000 persons aged 15 to 50 and by Hood and associates, who estimated the rate of 4.9 per 100,000 aged < 60 in Göteborg, Sweden.

It appears that the reduction in renal mortality rates has resulted from both changes in diagnostic habits and the effects of competing mortality. However the magnitude of the reduction in deaths from chronic nephritis is so great that one is inclined to ascribe at least part of it to a true change in the pathogenesis of the chronic nephritides. If the decrease in deaths from acute poststreptococcal glomerulonephritis can be taken as an indication of a similar decline in the incidence of this disease, a causal relation between poststreptococcal glomerulonephritis and chronic glomerulonephritis would explain the observations.

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REFERENCES

1. World Health Organization: Manual of the International Statistical Classification of diseases, injuries, and causes of death, Geneva, 1957, Vol. I, pp. 180 to 182.
2. Kessner, D. M., and Florey, C. du V.: Mortality trends for acute and chronic nephritis and infections of the kidney, Lancet 2:979, 1967.
3. Segi, H., Kurihara, M., and Tsukahara, Y.: Mortality for selected causes in 30 countries (1950-1961). Age-adjusted death rates and age-specific death rates, Tokyo, 1966, pp. 49-50.
4. United States Department of Health, Education, and Welfare: Vital statistics of the United States 1955. Supplement: Mortality data, multiple causes of death. U. S. Government Printing Office, 1965.
5. Mosbech, J.: The mortality from renal diseases in Denmark, Danish Med. Bull. 7:38, 1960.
6. Hood, B., Falkheden, T., and Carlson, M.: Trends and present patterns of mortality in chronic uremia, Acta med. scandinav. 181:561, 1967.
7. Schreiner, G. E.: The nephrotoxicity of analgesic abuse, Ann. Int. Med. 57:1047, 1962.
8. Morrin, P. A. F.: A survey of chronic renal failure in Southeastern Ontario, Canada M. A. J. 94:1353, 1966.

Hypolipidemia in anemia

Following Erben's[1] description, in 1902, of low cholesterol levels in chlorosis, there appeared numerous reports of hypocholesterolemia in pernicious anemia, and in other anemias such as so-called secondary anemia, Banti's syndrome or splenic anemia, acholuric jaundice and in myeloid or lymphatic leukemia. Hypophospholipidemia was also found in pernicious anemia. In 1931 Peters and van Slyke, wrote that "a general reaction to anemia was an excess of plasma neutral fat and fatty acids

and deficiency of cholesterol and phospholipids These reports seem to excite little attention although the association of hypolipidemia with anemia might have important implications for the epidemiology of atherosclerotic disease A confirmatory study was therefore undertaken.

In 26 subjects each with one of a variety of chronic anemias, the serum cholesterol level was low in almost every instance in 2 subjects it was less than 100 mg /100 ml and in 11 it lay between 100 to 150 mg./100 ml. In 5 of 9 male subjects, the level fell on or beyond the lower 95 or 99 per cent confidence limits of normal male subjects of corresponding age. Phospholipid levels, measured in 10 subjects, were also considerably reduced but fasting serum triglyceride levels were normal in the 6 subjects in whom they were measured Each of the 3 major plasma lipoprotein fractions of one fasting subject showed a proportionate reduction in cholesterol and phospholipid content

In 2 sibs with congenital microspherocytosis, with evidence of hemolysis but without anemia, serum cholesterol levels were also reduced (125 mg /100 ml. and 136 mg /100 ml respectively). Seven subjects with congenital microspherocytosis treated months or years previously by splenectomy had cholesterol and phospholipid levels which tended to be low but not to the same extent as in the anemic subjects, suggesting that although lipid levels rise after treatment of anemia they may not attain normal heights.

In another patient with congenital microspherocytosis, during the month following splenectomy the serum cholesterol level rose from 88 mg /100 ml to 169 mg /100 ml confirming earlier observations on the effect of splenectomy Similarly a prompt rise in serum cholesterol levels was seen in a subject with pernicious anemia after treatment with vitamin B_{12}, similar to the response obtained by others with liver extract

Anemia is prevalent in Western populations having been found in 50 per cent of women aged 18 to 55 years in Aberdeen, Scotland in 25 to 30 per cent of women aged 15 to 34 years in an English general practice over a 5 year period, and in 15 per cent of a sample of men and women in an English rural community Over the long period during which atherosclerosis develops, many women will be anemic and the present findings suggest, will have low cholesterol levels. Since serum cholesterol levels in women under the age of 50 years, directly relate to the risk of developing ischemic heart disease, anemia may contribute to the relative freedom from ischemic heart disease enjoyed by premenopausal women as compared with men of the corresponding age, or with postmenopausal women Similarly in some countries, a high rate of anemia may also relate to their low incidence of ischemic heart disease.

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REFERENCES

1 Erben, F Ueber die chemische Zusammensetzung des leukämischen Blutes, Ztschr klin. Med 47:302 1902
2 Peters, J P and van Slyke D D Quantitative clinical chemistry ed. 1 London 1931 Baillière Tindall & Cox, vol. IV
3 Williams, H. H., Erickson, B N Bernstein, S. S., and Macy I G Phospholipid partition (lecithin, cephalin and sphingomyelin) of blood in pernicious anemia and lipemia, Proc. Soc. Exper Biol. & Med. 45 151 1937
4. King J H Studies in the pathology of the spleen Arch. Int Med. 14 145 1914.
5 Bloor W R., and MacPherson, D J : The blood lipoids in anaemia, J Biol. Chem. 31 79 1917
6. MacAdam W and Shiskin C. The cholesterol content of the blood in anaemia and its relation to splenic function Quart J Med 15 193 1922.
7 Davidson L. S. P and Fullerton H W Chronic nutritional hypochromic anaemia, Edinburgh M J 45 1 1938.
8. Fry J Clinical patterns and course of anaemias in general practice, Brit. M J 2 1732, 1961
9 Kilpatrick, G S. Prevalence of anaemia in the general population Brit. M J 2 1736, 1961

Cardiac tamponade following external cardiac massage

External cardiac massage is an accepted and effective method for cardiac resuscitation. Multiple complications have been associated with external massage including fractures of ribs and sternum bone marrow emboli pneumothorax flail chest, subcutaneous emphysema, hemopericardium, hepatic lacerations pulmonary lacerations and gastric rupture Cardiac tamponade is a known complication following needle puncture of the heart and is secondary to continued bleeding into the pericardial space Hugh and Stephenson[1] discuss cardiac tamponade as a complication of open cardiac massage but to our knowledge it has not been described after closed-chest massage The

following case report documents cardiac tamponade as a reversible cause of inadequate cardiac output following cardiac resuscitation.

A 43-year-old Caucasian woman was admitted to the neurosurgical service of Cleveland Metropolitan General Hospital because of bitemporal headaches of months duration and grand mal seizure. Her physical examination was unremarkable. Routine laboratory studies were normal. The chest film demonstrated a normal heart and clear lung fields. The electrocardiogram (ECG) showed left axis deviation. The skull films, brain scan and left carotid arteriogram were all consistent with a sphenoid ridge meningioma. Because of uncontrolled seizures, the meningioma was excised through left frontoparietal craniotomy. She appeared alert and well during the first postoperative day. On the second day a left-sided seizure was followed by cardiac arrest. Resuscitation measures including external cardiac massage and an intracardiac injection of epinephrine were instituted. Ventricular fibrillation responded to electrical defibrillation, recurred, and required 2 subsequent conversions. Spontaneous respirations returned but she remained unconscious. Ventricular tachycardia and hypotension ensued 45 minutes after arrest. Following electrical conversion to sinus tachycardia, the blood pressure was 110 systolic and gross paradoxical pulse was evident. The jugular venous pressure measured 21 cm. H_2O. Arterial blood pressure was soon unobtainable. Pericardiocentesis, using subxiphoid approach, yielded 130 of pink serous fluid. This promptly led to return of recordable blood pressure (170/80), jugular venous pressure of 15 cm. H_2O and disappearance of the paradoxical pulse. Her vital signs stabilized and tamponade did not return, but she did not regain consciousness. The pericardial fluid had a hematocrit of 2 per cent negative gram stain, and sterile mycobacterial and bacterial cultures.

A postarrest chest film disclosed a left pleural effusion. Serial ECG demonstrated poor R-wave progression in Leads V but no ST or T wave abnormalities. The serum glutamic oxalacetic transaminase (SGOT) was 138 units 24 hours after arrest. She remained unconscious, developed left upper and lower lobe pneumonia, and died 5 days after the arrest. Postmortem examination confirmed the extensive pneumonia and revealed a recent fibrinous pericarditis and 50 c.c. of serosanguineous fluid. The pericardium and epicardium were not thickened and showed little inflammatory reaction except for occasional mononuclear and polymorphonuclear cells. Neuropathological examination of the brain revealed recent cerebral anoxia and total removal of the meningioma.

To our knowledge, cardiac tamponade has not been a reported complication of external cardiac massage. Tamponade occurring after needle puncture of the myocardium is secondary to continued bleeding. The pericardial fluid in this case contained little blood. Therefore, the acute tamponade may have been secondary to traumatic edema following external cardiac massage. The appearance of tamponade 45 to 60 minutes after initial resuscitation efforts and the elevated SGOT and normal serum glutamic pyruvic transaminase (SGPT) would be consistent with this interpretation.

Recognition of cardiac tamponade following resuscitation is of prime importance since it represents a readily reversible cause of hypotension and inadequate cardiac output.

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REFERENCES

1. Kaplan, B. M., and Knott, A. P.: Closed chest massage for circulatory arrest, Arch. Int. Med. 114:5, 1964.
2. Morgan, R. R.: Laceration of the liver from closed-chest cardiac massage, New England J. Med. 265:82, 1961.
3. Baringer, J. R., Salzman, E. W., Jones, W. L., and Friedlich, A. L.: External cardiac massage, New England J. Med. 265:62, 1961.
4. Demos, N. J., and Poticha, S. M.: Gastric rupture occurring during external cardiac resuscitation, Surgery 55:364, 1964.
5. Hugh, E., and Stephenson, J. R.: Cardiac arrest and resuscitation, St. Louis, 1964, The C. V. Mosby Company, p. 303.

Letter to the Editor

Supravalvular pulmonic stenosis

To the Editor

In the article entitled "Supravalvular Pulmonic Stenosis, Abnormal Facial Appearance, and Mental Retardation" (Am. Heart J. 75:340, 1968), Dr. Hartell and his associates report the ascending aortogram to demonstrate a normal aortic root. I would disagree with this interpretation and believe that the aortic root shows a moderate dilatation of the sinuses of Valsalva and the slightest suggestion of a supravalvular narrowing of the ascending aorta. In addition, I believe that there is a possibility that the aortic valve may be bicuspid, rather than tricuspid. I realize that I am working under the handicap of only one view of the ascending aortogram, but nevertheless the sinuses of Valsalva are distinctly dilated.

This dilatation of the sinuses of Valsalva is the type of finding one might expect in minimal degree of supravalvular aortic stenosis or degenerative lesion of the aortic media, such as Erdheim medionecrosis or the Marfan syndrome. In addition, one might find it in the syndrome of myxomatous degeneration of the aortic cusps.

I feel that this abnormality of the aortic root indicates that in this patient there is association of aortic root and pulmonic root abnormality of the type seen in supravalvular aortic stenosis (or the hypercalcemia syndrome) and not just pulmonary arterial changes alone.

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Reply

To the Editor

Dr. Layman has drawn attention to the configuration of the aortic root in our patient with supravalvular pulmonic stenosis (Am. Heart J. 75:340, 1968). We agree that the sinuses of Valsalva appear somewhat dilated, but it is known that these structures normally show some variation. It is inevitable that an aortic trunk rising from this type of sinus gives the impression of being narrowed. This is not the point we wanted to stress, however. Pressure tracings across this area revealed no gradients, and aortograms showed none of the types of constriction known to occur in men, i.e., hour-glass type, membraneous, or hypoplastic. Accordingly, we think that the term supravalvular aortic stenosis is irrelevant, even if labelled minimal. Moreover, a third aortic cusp is clearly visible in the original picture but is lost in the reproduction shown in the article.

Dr. Layman's comments on the possibility of degenerative lesions in the aortic wall are interesting, but in the absence of histological evidence they remain just speculations.

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Electrocardiograms and left ventricular hypertrophy

To the Editor

The excellent article by Romhilt and Estes in the June issue[1] is a valuable improvement in ECG recognition of LVH and provides a relatively simple point system to encompass the complexities of multiple criteria. The authors cited our work on the RV_6:RV_5 voltage ratio[2] as increasing their sensitivity to 66.7 per cent while only adding one false positive, but made the assumption that it could produce additional false positives in patients with emphysema or other causes of RVH with leftward QRS transition. The authors did not make clear that our criteria demanded a q wave in both V_5 and V_6 (producing qR, qRs, or qRS deflections). We excluded RS configurations. Since our original work, we have further confirmed and amplified the findings on the specificity of this ratio in all cases picked up from daily ECG recording.

With regard to emphysema, we have correlated ECG findings with degree of airway obstruction in 301 consecutive patients. In reviewing this material, RV_6 almost never exceeded RV_5, although with severe emphysema and very small r waves and rS this sometimes occurred. Since our criteria[2,3] call for initial q waves, we did not evaluate this material. Although LV wall thickening is common in our autopsied emphysema patients, indeed the progression of emphysema may well mask antecedent LVH.

In other causes of RVH, even RSV_6 exceeding RSV_5 is not common in our experience except in ventricular septal defect, let alone other leftward QRS transitions. This appears to accord with theoretical and practical[4] considerations. (Indeed, we have since collected patients with RS deflections and found larger RSV_6 to be uncommon but usually found it in patients with LVH or combined hypertrophy.) Probably the fact that the V_6 elec-

trode position is posterior to all the other precordial positions accounts for such findings.

REFERENCES

1. Romhilt D W and Estes, E. H J A point score system for the ECG diagnosis of left ventricular hypertrophy Am. Heart J 75 752, 1968.
2. Holt, D H., and Spodick, D H. The RV RV ratio in left ventricular hypertrophy Am. Heart J 63:65 1962
3. Kumar S and Spodick, D H. Specificity of RV:RV in the E.C.G. recognition of left ventricular hypertrophy Dis. Chest 50:519 1966.
4. Spodick, D H., Hauger J H Tyler J H., Muench, H and Dorr C. A.: The electrocardiogram in pulmonary emphysema Relationship to degree of airway obstruction, Am Rev Resp. Dis. 88 14 1963.
5. Scott, R C. Evolving hypertrophy patterns, J Electrocardiol. 1:97 1968.
6. Brown, F K Brown, W J Ellison, R. G and Hamilton, W F Electrocardiographic changes during development of right ventricular hypertroph in the dog Am. J Cardiol 21:223 1968.
7. Schamroth, L. The electrocardiographic manifestations of right ventricular dominance, South African M J 41 119 1967

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Reply

To the Editor

Dr Spodick observation that the specificity of the RV RV voltage ratio is mai tained when pplied to patient with mphysema, and R V H makes this criterion logical and useful addition to the point score system as three-point criterion. Ou reservations lay in the fact that such cases had been systematically excluded from our series. I am also grateful t him for emphasizing the morphologic component of this criterion which was not spelled out in ou article

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Book reviews

Electrophysiology and Ultrastructure of the Heart. Edited by Toyomi Sano, M.D., Vincent Mizuhira, M.D., and Kojiro Matsuda, M.D. New York and London, 1967, Grune & Stratton, Inc. 267 pages. Price $13.50.

This book consists of 19 relatively short papers based upon a special electrophysiology meeting held in Japan in September 1965 in association with the 23rd International Congress of the Physiological Sciences. The papers are clearly presented and nicely illustrated. The presentations are interesting and important. The electron micrographs are numerous and clear. Interesting subjects are presented such as the fine structure of the heart in the goldfish and the electrocardiogram of the goldfish obtained from an esophageal lead. The fine structure of the heart of the lovebird, goat, rabbit, monkey, mouse, dog, and man is also discussed. The similarities among the animals are outstanding. The fine structure of the conduction system is also rather extensively discussed and illustrated. The greatest part of the book is concerned with the membrane potential and the use of the microelectrodes, including myocardial cells grown in tissue culture. This is a very good book.

The Transplanted Heart. By Peter Hawthorne. Chicago, New York, and San Francisco, 1968, Rand McNally & Company. 192 pages. Price $4.95.

This book is for the layman. The author obviously has attempted to capitalize on the publicity of the cardiac transplant. He attempts to interpret the significance of the transplant of a human heart into another person for the lay reader while the medical and scientific world is still debating. He also describes many aspects of this undertaking. He describes Barnard, his associates, the hospital, patients and their relatives for the lay reader in a dramatic fashion. This is all done by a freelance journalist who is not a scientist but a [illegible] [illegible]. As long as the reader remembers the author is not a scientist nor a practicing physician or even a professional science writer, the reader may find this book to satisfy his curiosity. The book is not totally scientifically accurate. Hawthorne, like many other journalists, has dramatized an event which involves many important facets related to moral and ethical responsibilities to medically innocent, misinformed, and sick patients with whom a tradition of doctor-patient relationship has existed for centuries. This book obviously was written in great haste and is not interesting to a physician. Most of the material has appeared in the news papers.

Lehrbuch der Röntgendiagnostik (Textbook of Diagnostic Roentgenology). Vol. IV. Heart and Great Vessels, ed. 6. Lissner, J., Prof. Dr. med., Oberarzt der Universitätsklinik für Strahlentherapie und Nuklearmedizin, Frankfurt/M.; Scad, N., Pri. Doz. Dr. med., Röntgendiagnostisches Zentralinstitut der Universität Zurich, Kantonsspital; Thrun, P., Prof. Dr. med., Direktor des Instituts für Röntgenologie und Strahlenheilkunde der Universität Bonn; Wellauer, J., Prof. Dr. med., Direktor des Röntgendiagnostischen Zentralinstituts der Universität Zurich, Kantonsspital. Stuttgart, 1968, Georg Thieme Verlag. A volume of 558 pages with 1,353 illustrations.

This text is one of a six volume series on diagnostic roentgenology which has been a standard reference work in Europe since the first edition in 1928. This work was started by Dr. H. R. Schinz, of Zurich, Switzerland, and his collaborators. Previous editions have been translated into English, Italian, Spanish, and French.

The coverage of the various portions of the field of cardiac disease is quite extensive. There is a thorough discussion of the normal heart in various roentgenographic projections. Following this, there are large sections on congenital heart disease, including anomalies of the coronary arteries, aorta, and great veins.

There is less extensive but rather thorough handling of acquired heart disease, including valvular conditions and diseases of the myocardium, coronary arteries and pericardium, cardiac tumors, hypertension, arteriovenous fistula, cor pulmonale, trauma, and acquired diseases of the aorta. A short discussion is devoted to the use of electrokymography in diseases of the heart and great vessels.

The illustrations are black-on-white as opposed to the usual white-on-black background seen in most American journals and books. However, one may become accustomed to this after a while and the illustrations are of very good quality and carefully selected to show the many roentgen appearances which may be seen in cardiac conditions. On some of the pages, there may be as many as 12 small roentgenographic reproductions, each of which is shown with enough detail to illustrate the desired point.

There is no question that this text will remain one of the standard references in diagnostic roentgenology. For those who do not read German, it is my understanding that some of the other volumes have already been translated into English and that this volume should be translated into English some time during the coming year. The monograph is strongly recommended for both diagnostic roentgenologists and [illegible]ologists.

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